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Teratogenesis, perinatal, and neurodevelopmental outcomes after in utero exposure to antiseizure medication: Practice guideline from the AAN, AES, and SMFM

Alison M. Pack, MD, MPH[1]; Maryam Oskoui, MD, MSc[2]; Shawniqua Williams Roberson, MEng, MD[3]; Diane K. Donley, MD[4]; Jacqueline French, MD[5]; Elizabeth Gerard, MD[6]; David Gloss, MD, MPH&TM[7]; Wendy R. Miller, PhD, RN, CCRN[8]; Heidi M. Munger Clary, MD, MPH[9]; Sarah S. Osmundson, MD, MS[3]; Brandy McFadden[10]; Kaitlyn Parratt, MBBS (Hons 1)[11]; Page B. Pennell, MD[12]; George Saade, MD[13]; Don B. Smith, MD[14]; Kelly Sullivan, PhD[15]; Sanjeev V. Thomas, MD[16]; Torbjorn Tomson, MD[17]; Mary Dolan O'Brien, MLIS, PMP[18]; Kylie Botchway-Doe,[18]; Heather Silsbee, MWC[18]; Mark Keezer, MD, PhD[19]

1. Department of Neurology, Columbia University, New York City

2. Departments of Pediatrics and Neurology & Neurosurgery, McGill University, Montreal, Quebec

3. Department of Obstetrics and Gynecology, Vanderbilt University, Nashville, TN

4. Northern Michigan Neurology and Munson Medical Center, Traverse City, MI

5. Department of Neurology, NYU Grossman School of Medicine, New York City

6. Feinberg School of Medicine, Northwestern University, Chicago, IL

7. The NeuroMedical Center, Baton Rouge, LA

8. Epilepsy Foundation, Bowie, MD

9. Department of Neurology, Wake Forest University School of Medicine, Winston-Salem, NC

10. My Epilepsy Story, Nashville, TN

11. Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, NSW, Australia

12. Department of Neurology, University of Pittsburgh School of Medicine, PA

13. Department of Ob-Gyn, Eastern Virginia Medical School, Norfolk

14. Department of Neurology, University of Colorado School of Medicine, Aurora

15. Department of Biostatistics, Epidemiology, and Environmental Health Sciences, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro

16. Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala State, India

17. Department of Clinical Neuroscience, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden

18. American Academy of Neurology, Minneapolis, MN

19. Centre Hospitalier de l'Université de Montréal Research Centre (CRCHUM), Canada

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Address correspondence to

American Academy of Neurology: guidelines@aan.com

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DISCLOSURES

A. M. Pack serves on the editorial board for the journal *Epilepsy Currents*, receives royalties from UpToDate, receives funding from the National Institutes of Health (NIH) for serving as coinvestigator and site PI for the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study, and receives funding from Bayer for serving as a co-investigator on a study on women with epilepsy initiating a progestin IUD. An immediate family member of Dr. Pack has received personal compensation for serving as an employee of REGENEXBIO.

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S. Williams Roberson receives research funding from the National Institute on Aging for a study related to ICU delirium and associated cognitive decline, serves on the editorial board for *Neurology Today*, and has a non-compensated relationship as a Physician Advisory Board Member with Epilepsy Foundation of Middle and Western Tennessee.

D. K. Donley's immediate family member has received compensation in the range of $10,000–$49,999 for serving as the vice president of Novello Physicians Organization.

J. French's institution has received research support from the Epilepsy Study Consortium, the Epilepsy Foundation (funded by UCB), GW Pharmaceuticals, the One8 Foundation, FACES (Finding a Cure for Epilepsy and Seizures), the National Institute of Neurological Disorders and Stroke (NINDS), Xenon, and Cerevel. Dr. French has received personal compensation in the range of $100,000–$499,999 for serving as a Chief Medical and Innovation Officer with the Epilepsy Foundation. Dr. French has had a non-compensated relationship serving as a consultant or scientific advisory board member for Alterity Therapeutics Limited, Angelini, Arvelle Therapeutics, Autifony Therapeutics Limited, Baergic Bio, Beacon Biosignals, Biogen,

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S. S. Osmundson's institution has received research support from the NIH.

B. McFadden serves as Executive Director for My Epilepsy Story and is uncompensated for this role, serves as an uncompensated member of the ELC Group, serves as an uncompensated patient advisor, serves as an uncompensated Patient-Centered Outcomes Research Institute (PCORI) Ambassador, and receives travel reimbursement from PCORI for attending meetings.

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editor, associate editor, or editorial advisory board member for Thieme Publishing. The institution of Dr. Saade has received research support from Sera Prognostics, and from NICHD for clinical obstetrics issues. Dr. Saade has received research support from the NIH for studies related to chronic hypertension and pregnancy, human placenta evaluation, and pregnancy and cardiovascular health. Dr. Saade has received honoraria for speaking engagements at multiple universities and has given expert testimony, prepared an affidavit, and acted as a witness for legal proceedings regarding preeclampsia.

D. Smith has received personal compensation in the range of $10,000–$49,999 for serving as an evidence-based medicine methodologist for the AAN.

K. Sullivan has received intellectual property interests from a discovery or technology relating to health care.

S. V. Thomas is deceased; to the best of our knowledge, the relevant disclosures are as follows: Dr. Thomas served as a PI of a pregnancy registry in India that has generated clinical data pertaining to the use of antiepileptic drugs during pregnancy, received honoraria for BMJ Masterclasses on epilepsy, and received research grants from the Indian government. Dr. Thomas received personal compensation in the range of $0–$499 for serving as an editor, associate editor, or editorial advisory board member for Wiley India, and served on the editorial board of the journal *Epilepsy Research*.

T. Tomson's institution has received personal compensation in the range of $500–$4,999 for serving on a scientific advisory or data safety monitoring board for Angelini and GW Pharmaceuticals. The institution of Dr. Tomson has received research support from Eisai, GSK, UCB, Bial, Sanofi, Angelini, GW Pharma, Teva Pharma, Zentiva, Accord, Ecu Pharm, SF Group, and Glenmark (for serving as a PI in the EURAP study and the International Antiepileptic Drugs and Pregnancy Registry). Dr. Tomson has received personal compensation in the range of $500–$4,999 for serving as a speaker with Angelini, Sanofi, Eisai, Sun Pharma, and UCB. Dr. Tomson has received funding from GSK for serving as a PI for a study on sudden unexpected death in epilepsy; has received research funding from Stockholm County Council; and has received research funding from the European Union and Nordforsk.

M. Dolan O'Brien was an employee of the AAN.

K. Botchway-Doe is an employee of the AAN.

H. Silsbee is an employee of the AAN.

M. Keezer's institution has received research support from UCB and Eisai. Dr. Keezer serves on the editorial board for the journals *Epilepsia* and *Neurology: Clinical Practice.* Dr. Keezer has received a salary award from the Fonds de Recherche du Québec Santé and research grants from

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GLOSSARY

AAN: American Academy of Neurology
AES: American Epilepsy Society
aHR: adjusted hazard ratio
ASM: antiseizure medication
ASD: autism spectrum disorder
CI: confidence interval
COI: conflicts of interest
GS: Guidelines Subcommittee
ICD-10: *International Classification of Disease, Tenth Revision*
IQ: intelligence quotient
MCM: major congenital malformation
MONEAD: Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study
NEAD: Neurodevelopmental Effects of Antiepileptic Drugs study
NTD: neural tube defect
OR: odds ratio
PD: prevalence difference
POR: prevalence odds ratio
PR: prevalence ratio
PWECP: people with epilepsy of childbearing potential
RMD: raw mean difference
RR: risk ratio
SD: standard deviation
SGA: small for gestational age
SMFM: Society for Maternal-Fetal Medicine

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INTRODUCTION

Epilepsy is one of the most common neurological disorders, affecting more than 50 million people worldwide. One in 5 of those affected are people of childbearing potential, based on extrapolations from the proportion of the 2022 US female population aged 15–45 years.[1] Infants born to people with epilepsy are at increased risk of major congenital malformations (MCMs), adverse perinatal outcomes, and adverse neurodevelopmental outcomes.[2] Multiple factors are associated with this risk, including genetic differences, environmental factors, seizure control, and intrauterine exposure to antiseizure medications (ASMs). The unadjusted birth prevalence of any MCM among children born to people without epilepsy is approximately 2.4% to 2.9%.[3] The role of folic acid supplementation in mitigating these risks is unclear. Optimizing the treatment of epilepsy is necessary to achieve the most favorable outcomes for persons with epilepsy and their offspring.

RATIONALE FOR THIS PRACTICE GUIDELINE

In 2009, the American Academy of Neurology (AAN) published the guideline "Practice Parameter update: Management issues for women with epilepsy—Focus on pregnancy: Teratogenesis and perinatal outcomes."[4] The authors concluded that treatment with valproic acid carries a higher risk of MCMs in the offspring of women with epilepsy than treatment with carbamazepine, phenytoin, and phenobarbital, especially if taken in polytherapy. The risk associated with other commonly used ASMs, such as levetiracetam or topiramate, was not evaluated due to limited evidence available at the time concerning their use during pregnancy. The authors concluded that treatment with valproic acid carried the highest risk of adverse cognitive outcomes in the offspring of women with epilepsy as compared to carbamazepine, although the risk of autism spectrum disorder (ASD) was not addressed, as this association was not yet reported in the literature. Infants exposed to any ASM in utero had a higher risk of being born small for gestational age (SGA), but there was no evidence of an increased risk of fetal death.

A separate 2009 practice guideline recommended that preconception folic acid supplementation "may be considered to reduce the risk of MCMs" but did not provide further guidance on the dosage of this supplementation.[5] Since 2009, new studies have been published related to the risk of MCMs associated with several ASMs, the association between different ASMs and adverse perinatal or neurodevelopmental outcomes, and the effect of folic acid supplementation.

While the 2009 guidelines described the affected population as "women with epilepsy," that phrasing does not recognize the important difference between biological sex and sociocultural gender. In this update, we refer to the affected population with the gender-neutral language "people with epilepsy of childbearing potential" (PWECP).

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In this practice guideline update, we aim to provide guidance to clinicians when choosing a particular ASM, in monotherapy or polytherapy, in this patient population. We also aim to clarify the potential role of folic acid supplementation among PWECP. This guideline specifically addresses the following 4 clinical questions.

Clinical Questions

1. What is the prevalence of MCMs associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high doses vs low-medium doses of ASMs, in children born to PWECP?

2. What is the prevalence of adverse perinatal outcomes associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high doses vs low-medium doses of ASMs, in children born to PWECP?

3. What is the prevalence of adverse neurodevelopmental outcomes associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high vs low-medium doses of ASMs, in children born to PWECP?

4. What is the effect of intrauterine exposure to folic acid on the prevalence of MCMs, adverse perinatal outcomes, and neurodevelopmental outcomes, and how does this vary by folic acid dose in children born to PWECP treated with ASMs?

DESCRIPTION OF THE ANALYTIC PROCESS

In March 2018, the AAN Guidelines Subcommittee (GS) recruited a multidisciplinary panel consisting of AAN clinician members as well as American Epilepsy Society (AES), Society for Maternal-Fetal Medicine (SMFM), and patient representatives to develop this practice guideline project protocol, which was modified over time to include additional members. The final author panel includes content experts (EG, KP, SVT, and TT), methodology experts (MO and DBS), past and present AAN GS members (DKD, JF, KS, MK, SWR, and AMP), an AAN epilepsy quality measure workgroup representative (HMC), AES physician representatives (DG and PBP), SMFM physician representatives (SSO and GS), and patient representatives (WRM and BM). All panel members were required to submit online disclosure forms and copies of their curriculum vitae.

The panel leadership at the time of panel formation, consisting of the lead developer (CH), the AAN methodologist (DG), and the AAN staff person (SM), reviewed the disclosure forms and curriculum vitae for financial and intellectual conflicts of interest (COI). These documents were screened specifically to exclude both those individuals with a clear financial conflict and those whose professional and intellectual bias would diminish the credibility of the review in the eyes of the intended users. Dr. Cynthia Harden was the initial lead developer on this guideline and had

no conflicts of interest at the time the project was initiated in March of 2018. In September of 2018, she accepted a new employment position with Xenon Pharmaceuticals, making her ineligible to continue to serve on the guideline development panel per the AAN clinical practice guideline development process manual.[6] Because of this conflict, she recused herself from further participation on the panel and Dr. Alison M. Pack was appointed as the new lead developer. In accordance with AAN policy, the current lead developer (AMP) has no COI. Five of the 19 guideline developers (JF, EG, KP, GS, and TT) were determined to have COI, but each COI was judged to be not significant enough to preclude these developers from authorship. The developers determined to have COI did not review or rate the evidence. These individuals were consulted in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. They also participated in the recommendation development process. Because the panel majority (DKD, DG, DBS, MK, WRM, HMC, SO, AP, BM, MO, PBP, SWR, KS, and SVT) is free of COI, the entire panel voted on the guideline recommendations. The full panel was solely responsible for the final decisions about the design, analysis, and reporting of the systematic review and subsequent practice guideline, which were then submitted for approval to the AAN GS, the AES Guidelines & Assessment Committee, and the SMFM Publications Committee.

This evidence-based practice guideline update follows the methodology described in the 2017 edition of the AAN's guideline development process manual.[6] We summarize the process here.

Study Screening and Selection Criteria

Types of studies

Reviews, meta-analyses, and case reports were excluded, as were studies with 20 or fewer participants. Study eligibility was not limited by the language of the publication.

Types of participants

We included studies of PWECP aged 18 years or older. If a study included data combining adults and children, we included the study if those data exclusive to adults could be extracted separately, or if at least 90% of those included were aged 18 years or older. From the identified studies, none were excluded based on this criterion. If a study included data on people without epilepsy, we included the study if data on PWECP could be extracted separately or if at least 90% of those included were PWECP. Several pregnancy cohorts had numerous publications with potentially overlapping participants. We retained the most recent study that included the widest range of birth cohorts whenever possible. All pregnancy cohorts were included as less than 20% of participants overlap across these cohorts (e.g., International Registry of Antiepileptic Drugs and Pregnancy [EURAP][7] and the UK and Ireland Epilepsy and Pregnancy registry).[8] We use the terms "child" and "children" to refer to offspring of PWECP, irrespective of their age.

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Types of exposures

We included studies of PWECP who were exposed to at least 1 ASM in pregnancy whether in monotherapy or polytherapy, and both with or without preconception folic acid supplementation. The dose for an ASM exposure was classified as low-medium (low in the case of folic acid) or high according to the criteria presented by the relevant primary study, resulting in thresholds that varied between studies. This dose was the pre-pregnancy dose of the ASM. According to these studies, a high dose of valproic acid was defined as from 1,000 mg to more than 1,500 mg daily, a high dose of carbamazepine was from 700 mg to more than 1,000 mg daily, a high dose of lamotrigine was from 200 mg to more than 400 mg daily, and a high dose of phenobarbital was from 60 mg to more than 150 mg daily. Most studies defined a daily dose of preconception folic acid lower than 0.4 mg as none or insufficient and defined a high dose of folic acid as greater than or equal to 5 mg daily. Doses that were not otherwise classified as high were classified as low-medium (low in the case of folic acid).

Types of outcome measures

All comparisons were between PWECP who were treated with at least one ASM. We did not consider comparisons to people without epilepsy or to those not treated with an ASM because our clinical questions involved the comparison of ASMs and ASM doses.

Any consequences of intrauterine exposure to ASMs or folic acid are assumed to be present at the time of birth, irrespective of whether they are measured during the first weeks of life or remote from the time of birth. For any congenital birth defect, including MCMs, it is recommended that the frequency of this event be referred to as the live birth prevalence.[7] Using the term "incidence" is discouraged given that the total number of individuals at risk of the outcome at the onset of exposure (a requirement for the calculation of incidence) cannot be determined given the possibly high number of pregnancies that end before the pregnant person or medical team are aware that the pregnancy had existed. Of note, live birth prevalence may still be affected by survival bias, a form of selection bias, if the exposure and the outcome each influence the probability that a fetus survives until birth. All prevalence estimates reported in this systematic review will be per 1,000 live births. When extracting and reporting the results of adjusted analyses, we retained the term used by the primary study authors (e.g., risk ratio [RR] or odds ratio [OR]) rather than translating these into prevalence ratios (PRs) and prevalence odds ratios (PORs).

The proportion of affected exposed newborns with any MCM was extracted from each study. We defined MCMs as structural or functional anomalies that are of prenatal origin, are present at birth, and have significant adverse medical, social, or cosmetic consequences. We considered 6 specific MCM categories by consensus of the author panel: neural tube, brain, cardiac, renal, oral cleft, and urogenital/hypospadias. Malformations of the neural tube include brain malformations, but some studies additionally reported brain malformations as a separate category. For all of

these proportions, we extracted the unadjusted prevalence and calculated the difference in proportion (prevalence difference [PD]) with a 95% confidence interval (CI) for each potential ASM combination. We did not use the reported adjusted PR or POR for MCMs from the primary studies given that these used heterogeneous comparison groups that were often outside the scope of our 4 clinical questions. Limiting our review to only those studies that reported adjusted PR or POR for MCMs would have excluded many relevant primary studies from our evidence synthesis. Therefore, by using external comparisons to calculate our estimates of prevalence differences, these are anchored at low confidence in evidence regardless of the contributing study risk of bias.

For perinatal outcomes, the proportion of deliveries resulting in perinatal death, the proportion of children born SGA, and the proportion born prematurely (<37 weeks of gestation) were extracted. We also extracted the adjusted relative frequency (i.e., PR or POR) when available and reported these studies individually, comparing the frequency of adverse perinatal outcomes between ASM exposure groups.

For neurodevelopmental outcomes, we extracted the adjusted global intelligence quotient (IQ adjusted for the birth parent's IQ [commonly referred to as maternal IQ] and other variables considered important by the primary study authors) and verbal and non-verbal IQ. Maternal IQ has an important influence on child IQ.[8] Differences across ASMs were studied using raw mean difference (RMD) (95% CI). We pooled the Differential Ability Scale and Wechsler Intelligence Scale for Children scores as these are both standardized such that they are normally distributed, with a population mean of 100 points and 1 standard deviation (SD) being equal to 15 points. We also included clinical diagnosis of ASD when defined using the criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV* or *DSM-5*), by using *International Classification of Disease, Tenth Revision* (ICD-10) codes, or as identified by 15 positive responses or greater on the 40-item Social Communication Questionnaire. We extracted both the unadjusted prevalence and the adjusted relative frequency (i.e., PR or POR) whenever available, comparing the frequency of adverse neurodevelopmental outcomes between ASM exposure groups. When we conclude that "we found no studies reporting…," this reflects that there were no data amenable to our planned analyses, although there may have been data that are informative for related clinical questions. For all adjusted analyses, the variables included in the regression models were those deemed by the primary study authors to be most important. We used random effects meta-analysis (DerSimonian and Laird method) to pool prevalence estimates across studies. For each exposure-outcome pair, we included data from all selected studies, not exclusively the study with lowest risk of bias. We used the double arcsine transformation for the synthesis of prevalence data (with a sine-squared back transformation) to limit the pooled estimates to between 0 and 1.0, as well as to stabilize the variances.[99] We assessed heterogeneity using Cochrane's Q test and the I^2 coefficient. Heterogeneity was deemed present with a *p* value less than 0.05 or an I^2 coefficient greater than 50%.

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Systematic review of the evidence

The panel searched Ovid MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), Ovid Embase, CINAHL, the Database of Abstracts of Reviews of Effects (DARE), ClinicalTrials.gov, and the U.S. Food and Drug Administration (FDA) literature databases from June 1, 2007 to February 15, 2019 for relevant peer-reviewed articles that met inclusion criteria (see appendix 3 for the search strategies). The initial search after duplicates were removed yielded 4,039 articles. Two review panel members (not the same pair for all articles) independently reviewed the article titles and abstracts for potential relevance. Of the reviewed abstracts, 307 were identified as potentially relevant by either reviewer and the full text of these articles was obtained for review. Each of the 307 full-text articles were independently reviewed for relevance by 2 review panel members. If there were any initial disagreements about inclusion after the full-text review, consensus was achieved by discussion between the 2 panelists. A third reviewer was included to break any ties if consensus could not be achieved. One hundred and eighty-three full-text articles were selected and rated for risk of bias by 2 panel members using the AAN criteria for the classification of causation studies. Class I studies have the lowest risk of bias and Class IV studies have the highest risk of bias. As per pre-defined exclusion criteria that are laid out in the AAN's guideline development process manual,[6] the panel excluded articles that were assessed as Class IV level of evidence (n = 133). This left 50 articles for inclusion. Forty articles included in the 2009 guidelines were reviewed by 2 panel members and 19 were selected for inclusion (see figure 1), for a total of 69 articles.

An updated literature search was completed to identify additional relevant articles published between February 15, 2019, and August 1, 2022. The initial search after duplicates were removed yielded 128 articles. The abstracts and full-text articles were reviewed following the same process as the first literature review, which resulted in 13 articles being added to the systematic review.

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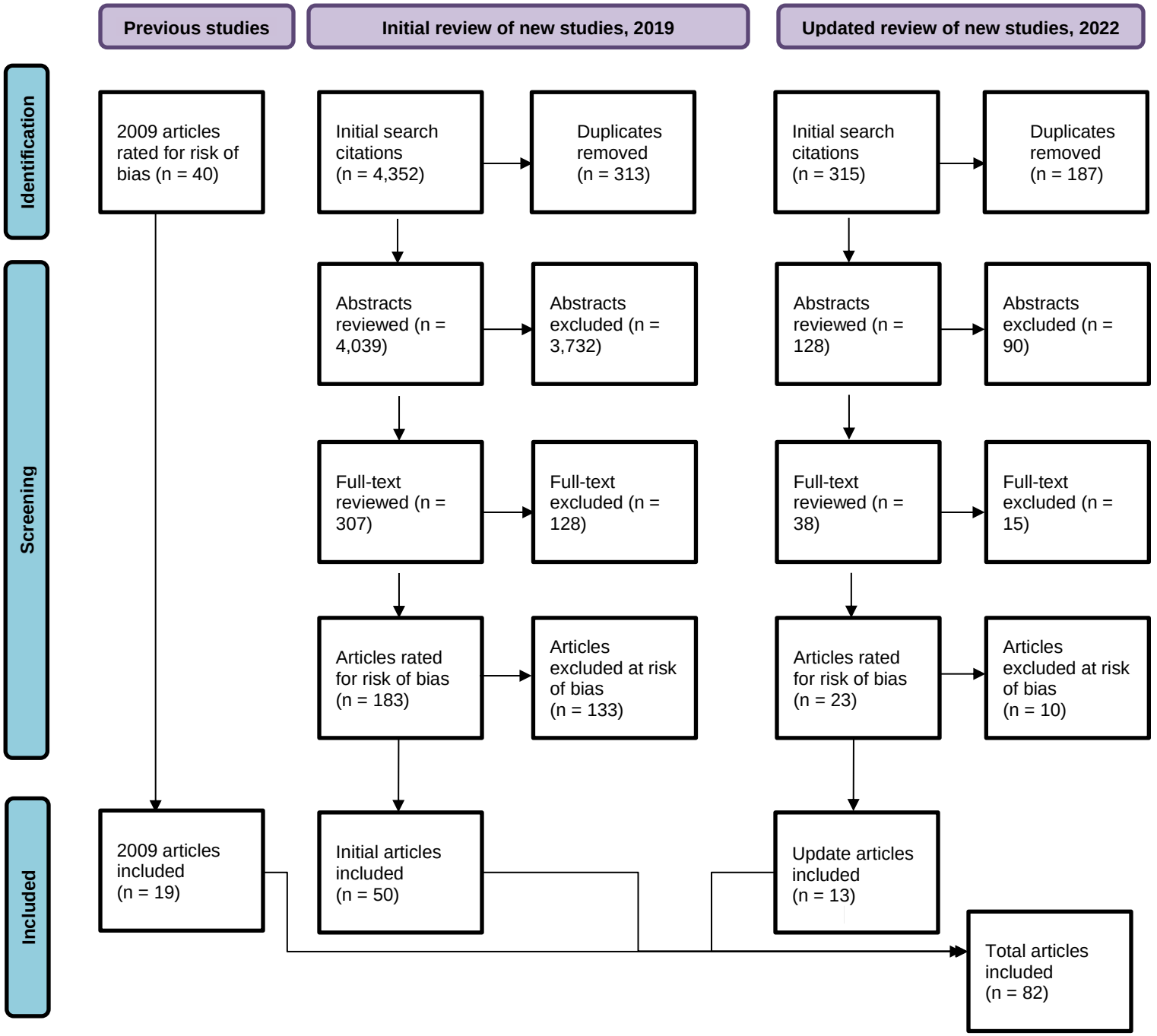
Figure 1. Study selection flow chart



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A modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was used to develop conclusions following the analysis of evidence (see the AAN's guideline development process manual for full details[6]). The evidence was analyzed based on various parameters pertaining to risk of bias, consistency, directness, precision, and publication bias, providing transparency of the classification of evidence. As all comparisons included indirect data (comparisons between results reported in different studies) and, at best, classified as Class III evidence to address causation, the initial confidence rating for most conclusions was anchored as low if at least 2 Class III or at least 1 Class I or II studies informed each estimate used in the comparisons. The initial confidence rating was set to very low if one of the contributing estimates was informed by a single Class III study.

In a second step, the classification of evidence was upgraded or downgraded according to criteria specified in the AAN's guideline development process manual (e.g., upgraded if large magnitude of effect, downgraded if lack of statistical precision).[6] For estimates obtained through indirect comparisons, confidence in the evidence was downgraded for precision when the width of the 95% CI for any PD for MCMs or ASD was greater than 100 per 1,000 live births, or greater than 300 per 1,000 live births for perinatal outcomes. Confidence in the evidence was also downgraded for precision when the width of the 95% CI for RMD for IQ was greater than 20 points. For indirect comparisons, although we present the PD in the synthesis of evidence and conclusions, our assessment of magnitude of effect was based on the corresponding PR. Confidence in the evidence was upgraded by 1 level for large magnitude of effect if the calculated PR was greater than 2 or lower than 0.5. Confidence in the evidence was upgraded by 2 levels for very large magnitude of effect if the calculated PR was greater than 10 or lower than 0.1. Confidence in the evidence was upgraded by 1 level for large magnitude of effect for IQ if the RMD was greater than 10 points and was upgraded by 2 levels if greater than 20 points. For estimates drawn from adjusted PR (relevant to the perinatal and neurodevelopmental outcomes), confidence in evidence was downgraded for precision if the width of the CI was greater than 2. If the confidence in the evidence was very low, it was not upgraded for other factors. Estimates not reaching statistical significance were not upgraded for magnitude of effect.

The author panel formulated a rationale for each recommendation based on the evidence systematically reviewed as well as stipulated axiomatic principles of care, related evidence, and inferences. This rationale transparently documents the deductive logic supporting each set of recommendation statements. Four types of premises can be used to support recommendations: (1) evidence-based conclusions from the systematic review, (2) generally accepted principles of care, (3) strong evidence from related conditions, and (4) deductive inferences from other premises. Recommendations must always be supported by at least one premise.[6] From this rationale, corresponding actionable recommendation statements were inferred. The level of obligation of each recommendation was assigned using a modified Delphi process that considered the following prespecified domains: the confidence in the evidence systematically reviewed, the acceptability of axiomatic principles of care, the strength of indirect evidence, and

the relative magnitude of benefit to harm. Additional factors explicitly considered by the author panel that could modify the level of obligation included judgments regarding the importance of outcomes, cost of compliance with the recommendation in relation to benefit, the availability of the intervention, and anticipated variations in patients' preferences. The level of obligation was indicated using standard modal operators. *Must* corresponds to Level A, which are very strong recommendations based on high confidence in the evidence and require both a high magnitude of benefit and low risk; *should* corresponds to Level B, which are strong recommendations; and *may* corresponds to Level C, which is the lowest allowable recommendation level the AAN considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation. The approach for arriving at a final recommendation is described in further detail in the AAN's guideline development process manual.[6]

ANALYSIS OF EVIDENCE

1. What is the prevalence of MCMs associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high doses vs low-medium doses of ASMs, in children born to PWECP?

The unadjusted birth prevalence of any MCM among children born to people without epilepsy is approximately 24 to 29 per 1000 births.[3] Forty-eight studies were identified examining the risk of MCMs among children exposed in utero to ASMs.[10-52] Of these, 31 studies[10, 12-14, 18, 22, 24-29, 33, 35, 37-46, 49, 51-56] reported on unique cohorts for any MCM with ASM monotherapy use and 16 studies[10, 14, 20, 22, 24, 27, 31, 34, 35, 37, 44, 45, 48, 54-56] reported on ASM polytherapy use. The unadjusted prevalence (reported as number of cases per 1,000 live births) of any MCM by ASM used in monotherapy or polytherapy is summarized in table 1. The effects of individual ASMs are pooled across 2 to 20 studies. Valproic acid is associated with the highest risk of any MCM in monotherapy, with a prevalence of 96.7 per 1,000 live births (95% CI 80.4–114.2). Phenobarbital and phenytoin have the next highest prevalence, with 60.3 (95% CI 47.1–75.0) and 51.3 (95% CI 35.9–69.2) per 1,000 live births, respectively. Topiramate and carbamazepine are associated with a lower prevalence of any MCM, with 44.5 (95% CI 30.9–60.4) and 43.7 (95% CI 35.7–52.6) per 1,000 live births, respectively. Oxcarbazepine (31.3 per 1,000 live births, 95% CI 21.6–42.8), lamotrigine (30.7 per 1,000 live births, 95% CI 25.4–36.4), levetiracetam (34.8 per 1,000 live births, 95% CI 19.5–54.3), and gabapentin (30.9 per 1,000 live births, 95% CI 5.5–76.1), are associated with the lowest prevalence of any MCM. Clobazam, clonazepam, ethosuximide, primidone, and zonisamide each had a small number of exposed individuals (from 64 to 187 participants). Data were not available for acetazolamide, ethosuximide, eslicarbazepine acetate, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, and vigabatrin.

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Table 1. Unadjusted prevalence of any MCM by ASM in monotherapy or polytherapy

ASM	Mono or polytherapy	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence between monotherapy and polytherapy (95% CI)
Carbamazepine	Monotherapy	9,908	69.6	2 Class I,[29, 41] 6 Class II,[10, 12, 18, 37, 39, 44] 11 Class III[13, 22, 35, 38, 43, 45, 46, 49, 51, 52, 56]	43.7 (35.7–52.6)	-14.9 (-38.1 to 8.3) Low confidence in evidence
	Polytherapy	1,231	59.3	3 Class II,[10, 37, 44] 5 Class III[20, 35, 45, 48, 51]	58.6 (38.8–82.1)	
Clobazam	Monotherapy	64	0	1 Class II[18]	31.3 (0.5–91.9)	-5.8 (-82.4 to 70.8) Very low confidence in evidence, downgraded for imprecision
	Polytherapy	27	0	1 Class II[44]	37.0 (29.2–152.2)	
Clonazepam	Monotherapy	187	26.5	3 Class III[35, 49, 52]	30.3 (7.4–67.8)	-56.2 (-113.3 to 1.0) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
	Polytherapy	126	0.0	1 Class II,[44] 2 Class III[35, 51]	86.4 (44.1–141.1)	
Ethosuximide	Monotherapy	NA	NA	NA	NA	NA
	Polytherapy	35	NA	1 Class II[44]	28.6 (22.4–118.6)	
Gabapentin	Monotherapy	90	0.0	2 Class II[25, 42]	30.9 (5.5–76.1)	NA
	Polytherapy	NA	NA	NA	NA	
Lamotrigine	Monotherapy	10,746	49.4	2 Class I,[29, 41] 4 Class II,[10, 12, 18, 25] 8 Class III[13, 14, 22, 35, 49, 52, 55, 56]	30.7 (25.4–36.4)	-13.9 (-26.4 to -1.4) Low confidence in evidence
	Polytherapy	1,421	4.8	1 Class II,[10] 4 Class III[14, 20, 35, 48]	44.6 (34.1–56.5)	
Levetiracetam	Monotherapy	2,248	77.8	1 Class I,[29] 3 Class II,[18, 24, 25] 6 Class III[27, 35, 53, 55-57]	34.8 (19.5–54.3)	-29.7 (-73.7 to 14.2) Low confidence in evidence, upgraded for magnitude of effect
	Polytherapy	605	67.0	1 Class II,[24] 3 Class III,[27, 35, 55] 2 Class IV[58, 59]	64.5 (30.1–110.8)	
Oxcarbazepine	Monotherapy	1,036	0.0	1 Class I,[29] 2 Class II,[18, 25] 2 Class III[35, 56]	31.3 (21.6–42.8)	-17.6 (-45.7 to 10.5) Low confidence in evidence
	Polytherapy	262	0.0	1 Class II,[44] 1 Class III[35]	48.9 (26.2–78.2)	
Phenobarbital	Monotherapy	1,116	0.0	1 Class I,[29] 3 Class II,[18, 39, 44] 5 Class III[35, 38, 43, 45, 56]	60.3 (47.1–75.0)	16.9 (-8.8 to 42.6) Low confidence in evidence
	Polytherapy	341	0.0	1 Class II,[44] 1 Class III[51]	43.4 (24.4–67.5)	

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Phenytoin	Monotherapy	1,604	52.3	2 Class I,[29, 41] 4 Class II,[18, 39, 42, 44] 8 Class III[38, 43, 45, 46, 49, 51, 52, 56]	51.3 (35.9–69.2)	13.3 (-13.4 to 40.1) Low confidence in evidence
	Polytherapy	318	0.0	1 Class II,[44] 2 Class III[48, 51]	38.0 (19.8–61.7)	
Primidone	Monotherapy	99	0.0	3 Class III[22, 38, 43]	101.5 (50.4–167.7)	NA
	Polytherapy	NA	NA	NA	NA	
Topiramate	Monotherapy	748	0.0	1 Class I,[29] 3 Class II,[18, 25, 42] 2 Class III[35, 52]	44.5 (30.9–60.4)	-26.9 (-110.2 to 56.3) Very low confidence in evidence, downgraded for imprecision
	Polytherapy	42	NA	1 Class III[35]	71.4 (9.3–17.2)	
Valproic acid	Monotherapy	5,658	67.0	2 Class I,[29, 41] 5 Class II,[10, 12, 18, 37, 44] 12 Class III[13, 22, 26, 35, 38, 43, 45, 49, 51-53, 56]	96.7 (80.4–114.2)	-5.1 (-32.6 to 22.5) Low confidence in evidence
	Polytherapy	1,262	34.8	4 Class II,[10, 37, 44, 60] 6 Class III[22, 34, 35, 45, 51, 56]	101.7 (81.0–124.5)	
Zonisamide	Monotherapy	116	87.7	1 Class II,[18] 1 Class III[54]	39.2 (11.7–236.1)	-18.9 (-142.3 to 104.4) Very low confidence in evidence, downgraded for imprecision
	Polytherapy	86	0.0	1 Class III[54]	58.1 (16.7–119.3)	

Note: No data were available for acetazolamide, brivaracetam, eslicarbazepine acetate, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin.

MCM = major congenital malformation; ASM = antiseizure medication; CI = confidence interval; NA = not applicable; I^2 = a statistical measure of study heterogeneity

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The unadjusted prevalence (reported as number of cases per 1,000 live births) of any MCM for each ASM used in polytherapy are also summarized in table 1. The effects of individual ASMs are pooled across 1 to 19 studies. The difference in MCM prevalence between monotherapy and polytherapy use of carbamazepine, clobazam, clonazepam, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide did not reach statistical significance. Of the remaining comparisons, intrauterine exposure to monotherapy had a lower prevalence of any MCM per 1,000 live births compared to polytherapy exposure for lamotrigine (PD -13.9, 95% CI -26.4 to -1.4). Data were not available to compare polytherapy to monotherapy use for acetazolamide, eslicarbazepine acetate, ethosuximide, gabapentin, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, primidone, rufinamide, stiripentol, tiagabine, or vigabatrin.

We calculated PD per 1,000 live births (95% CI) between each possible pairing of ASMs used in monotherapy (table 2). The prevalence of any MCM per 1,000 live births was greater with carbamazepine exposure compared to lamotrigine (PD 13, 95% CI 3–23). The prevalence of any MCM was greater with exposure to phenobarbital compared to exposure to carbamazepine (PD 16.6, 95% CI 0.3–32.9), lamotrigine (PD 29.6, 95% CI 14.6–44.6), levetiracetam (PD 25.5, 95% CI 3.2–47.8), and oxcarbazepine (PD 29.0, 95% CI 11.5–46.5). The prevalence of any MCM was greater with exposure to phenytoin compared to exposure to lamotrigine (PD 20.6, 95% CI 3.1–38.1) and oxcarbazepine (PD 20, 95% CI 0.3–39.7). The prevalence of any MCM was greater with exposure to primidone compared to clonazepam (PD 71.3, 95% CI 5.3–137.3), gabapentin (PD 70.6, 95% CI 2.1–139.1), lamotrigine (PD 70.8, 95% CI 11.9–129.7), levetiracetam (PD 66.7, 95% CI 5.5–127.9), and oxcarbazepine (PD 70.2, 95% CI 10.6–129.8). The prevalence of any MCM was greater with exposure to valproic acid compared to exposure to carbamazepine (PD 53.0, 95% CI 34.1–71.9), clobazam (PD 65.4, 95% CI 16.7–114.2), clonazepam (PD 66.5, 95% CI 31.9–101.1), gabapentin (PD 65.8, 95% CI 26.7–104.9), lamotrigine (PD 66.0, 95% CI 48.2–83.8), levetiracetam (PD 61.9, 95% CI 37.6–86.2), oxcarbazepine (PD 65.4, 95% CI 45.5–85.3), phenobarbital (PD 36.4, 95% CI 14.5–58.3), phenytoin (PD 45.4, 95% CI 21.7–69.1), and topiramate (PD 52.2, 95% CI 29.8–74.6), and the prevalence difference did not reach significance for zonisamide or primidone.

Table 2. Unadjusted prevalence differences of any MCM across ASMs in monotherapy (Next Page)

ASM			Carbamazepine	Clobazam	Clonazepam	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Primidone	Topiramate	Valproic acid	Zonisamide
	Prevalence per 1,000		**43.7**	**31.3**	**30.2**	**30.9**	**30.7**	**34.8**	**31.3**	**60.3**	**51.3**	**101.5**	**44.5**	**96.7**	**39.2**
		95% CI	35.6–52.6	0.5–91.9	7.4–67.8	5.5–76.1	25.4–36.4	19.5–54.3	21.6–42.8	47.1–75.0	35.9–69.2	50.4–167.7	30.9–60.4	80.4–114.2	11.7–236.1
Carbamazepine	**43.7**	35.6–52.6	X	-12.5 (-58.9 to 34) Low confidence	-13.5 (-44.9 to 17.9) Low confidence	-12.8 (-49.1 to 23.5) Low confidence	**-13 (-23.1 to -2.9) Low confidence**	-8.9 (-28.3 to 10.5) Low confidence	-12.4 (-26 to 1.2) Low confidence	**16.6 (0.3–32.9) Low confidence**	7.6 (-11.1 to 26.3) Low confidence	57.8 (-1.5 to 117.1) Very low confidence	0.8 (-16.2 to 17.8) Low confidence	**53 (34.1–71.9) Moderate confidence**	-4.5 (-117 to 108) Very low confidence
Clobazam	**31.25**	0.5–91.9		X	-1.1 (-55.8 to 53.7) Very Low confidence	-0.4 (-58.1 to 57.4) Very low confidence	-0.6 (-46.6 to 45.5) Low confidence	3.5 (-45.3 to 52.4) Low confidence	0.1 (-46.8 to 46.9) Low confidence	29 (-18.7 to 76.8) Low confidence	20 (-28.6 to 68.7) Low confidence	70.2 (-4.1 to 144.6) Very low confidence	13.2 (-34.8 to 61.3) Low confidence	**65.4 (16.7–114.2) Moderate confidence**	8 (-113.2 to 129.1) Very low confidence
Clonazepam	**30.2**	7.4–67.8			X	0.7 (-45.8 to 47.2) Low confidence	0.5 (-30.2 to 31.2) Low confidence	4.6 (-30.3 to 39.5) Low confidence	1.1 (-30.9 to 33.1) Low confidence	30.1 (-3.2 to 63.4) Low confidence	21.1 (-13.4 to 55.6) Low confidence	**71.3 (5.3–137.3) Very low confidence**	14.3 (-19.3 to 47.9) Low confidence	**66.5 (31.9–101.1) Moderate confidence**	9 (-107.2 to 125.2) Very low confidence
Gabapentin	**30.9**	5.5–76.1				X	-0.2 (-35.9 to 35.5) Low confidence	3.9 (-35.5 to 43.3) Low confidence	0.4 (-36.5 to 37.3) Low confidence	29.4 (-8.6 to 67.4) Low confidence	20.4 (-18.6 to 59.4) Low confidence	**70.6 (2.1–139.1) Very low confidence**	13.6 (-24.7 to 51.9) Low confidence	**65.8 (26.7–104.9) Moderate confidence**	8.3 (-109.3 to 125.9) Very low confidence
Lamotrigine	**30.7**	25.4–36.4					X	4.1 (-14.1 to 22.3) Low confidence	0.6 (-11.3 to 12.5) Low confidence	**29.6 (14.6–44.6) Low confidence**	**20.6 (3.1–38.1) Low confidence**	**70.8 (11.9–129.7) Very low confidence**	13.8 (-1.9 to 29.5) Low confidence	**66 (48.2–83.8) Moderate confidence**	8.5 (-103.8 to 120.8) Very low confidence
Levetiracetam	**34.8**	19.5–54.3						X	-3.5 (-23.9 to 16.9) Low confidence	**25.5 (3.2–47.8) Low confidence**	16.5 (-7.6 to 40.6) Low confidence	**66.7 (5.5–127.9) Very low confidence**	9.7 (-13.1 to 32.5) Low confidence	**61.9 (37.6–86.2) Moderate confidence**	4.4 (-109.1 to 117.9) Very low confidence

Oxcarbazepine	**31.3**	21.6–42.8							X	**29 (11.5–46.5) Low confidence**	**20 (0.3–39.7) Low confidence**	**70.2 (10.6–129.8) Very low confidence**	13.2 (-5 to 31.4) Low confidence	**65.4 (45.5–85.3) Moderate confidence**	7.9 (-104.8 to 120.6) Very low confidence
Phenobarbital	**60.3**	47.1–75.0								X	-9 (-30.7 to 12.7) Low confidence	41.2 (-19.1 to 101.5) Very low confidence	-15.8 (-36.1 to 4.5) Low confidence	**36.4 (14.5–58.3) Low confidence**	-21.1 (-134.2 to 92) Very low confidence
Phenytoin	**51.3**	35.9–69.2									X	50.2 (-10.8 to 111.2) Very low confidence	-6.8 (-29 to 15.4) Low confidence	**45.4 (21.7–69.1) Low confidence**	-12.1 (-125.5 to 101.3) Very low confidence
Primidone	**101.5**	50.4–167.7										X	-57 (-117.5 to 3.5) Very low confidence	-4.8 (-65.8 to 56.2) Very low confidence	-62.3 (-188.9 to 64.3) Very low confidence
Topiramate	**44.5**	30.9–60.4											X	**52.2 (29.8–74.6) Moderate confidence**	-5.3 (-118.5 to 107.9) Very low confidence
Valproic acid	**96.7**	80.4–114.2												X	-57.5 (-171 to 56) Very low confidence

Bold values are statistically significant

Prevalence difference = row - column

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The unadjusted prevalence of any MCM with exposure to high doses vs low-medium doses of each ASM are summarized in table 3. These data were obtained from 7 studies with indirect comparisons.[12, 22, 25, 29, 37, 48, 56] For valproic acid, there was a statistically significant and clinically important increase in the prevalence of MCMs with high vs low-medium doses (PD 166.7, 95% CI 63.3–270.2). A smaller difference in prevalence by dose was observed for phenobarbital (PD 84.3, 95% CI 20.6–148.0). A dose effect did not reach statistical significance for carbamazepine, lamotrigine, or phenytoin, though the estimates lacked precision.

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Table 3. Unadjusted prevalence of any MCM between high dose and low-medium dose for each ASM in monotherapy

ASM	Dose (range)	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence between high and low-medium dose ASM (95% CI)
Valproic acid	Low-medium (<700 to 1,500 mg/d)	1,733	3.4	1 Class I,[29] 2 Class II,[12, 37] 3 Class III[22, 48, 56]	64.4 (53.1–76.8)	166.7 (63.3–270.2) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
	High (1,000 to >1500 mg/d)	525	82.4	1 Class I,[29] 2 Class II,[12, 37] 3 Class III[22, 48, 56]	231.2 (136.5–342.1)	
Carbamazepine	Low-medium (<400 to 1,000 mg/d)	3,106	71.7	1 Class I,[29] 2 Class II,[12, 37] 1 Class III[56]	34.3 (23.0–47.8)	18.2 (-21.5 to 57.9) Low confidence in evidence
	High (700 to >1,000 mg/d)	1,043	80.7	1 Class I,[29] 2 Class II,[12, 37] 1 Class III[56]	52.5 (21.3–96.6)	
Lamotrigine	Low-medium (<200 to 325 mg/d)	3,799	59.3	1 Class I,[29] 2 Class II,[12, 25] 1 Class III[56]	28.4 (19.5–38.9)	9.3 (-5.2 to 23.8) Low confidence in evidence
	High (200 to >400 mg/d)	1,194	0.0	1 Class I,[29] 2 Class II,[12, 25] 1 Class III[56]	37.7 (27.6–49.2)	
Phenobarbital	Low-medium (<60 to 150 mg/d)	152	0.0	1 Class I,[29] 1 Class III[56]	32.1 (10.2–65.8)	84.3 (20.6–148.0) Very low confidence in evidence, downgraded for imprecision
	High (60 to >150 mg/d)	118	0.0	1 Class I,[29] 1 Class III[56]	116.5 (65.3–180.0)	
Phenytoin	Low (<200 mg /d)	68	0.0	1 Class III[56]	79.6 (27.8–154.8)	-31.8 (-117.4 to 53.9) Very low confidence in evidence, single study and imprecision
	High (>200 mg/d)	51	0.0	1 Class III[56]	47.8 (7.0–122.1)	

MCM = major congenital malformation; ASM = antiseizure medication; CI = confidence interval; NA = not applicable; I^2 = a statistical measure of study heterogeneity

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When considering specific MCMs (table 4) 23 studies[10, 14-19, 21, 23, 25, 31, 35, 36, 41, 42, 44, 45, 49, 51, 56, 61-63] were included. Phenytoin was associated with the highest prevalence of brain MCMs (27.4 per 1,000 live births, 95% CI 1.3–85.4), although this is based on only 56 participants and therefore the estimate lacks precision when using external comparisons to carbamazepine, lamotrigine, and valproic acid. Valproic acid was associated with the second highest prevalence of brain malformation (8.0 per 1,000 live births, 95% CI 2.5–16.5), and no prevalence difference was found compared to exposure to carbamazepine (PD -6.5, 95% CI -14.3 to 1.3), lamotrigine (PD 5.2, 95% CI -12.4 to 2.0) or phenytoin (PD 19.4, 95% CI -23.2 to 62.1).

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Table 4. Unadjusted prevalence of specific MCMs by individual ASMs in monotherapy

	ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence compared to reference (95% CI)
Brain						
	Carbamazepine	1,028	48.5	1 Class II,[10] 1 Class III[35]	1.5 (0.0–6.8)	-24.1 (-104.9 to -3.7) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
	Lamotrigine	4,548	0.0	1 Class I,[41] 2 Class II,[10, 25] 4 Class III[14, 15, 19, 35]	2.8 (1.5–4.5)	-22.8 (-103.6 to -2.9) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
	Phenytoin	56	NA	1 Class I[41]	27.4 (1.3–85.4)	Reference
	Valproic Acid	616	0.0	1 Class I,[41] 1 Class II,[10] 1 Class III[35]	8.0 (2.5–16.5)	-17.6 (-98.5 to 4.9) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
Neural tube						
	Carbamazepine	3,874	50.0	2 Class II,[18, 42] 5 Class III[21, 45, 49, 51, 56]	5.6 (2.6–9.7)	-8.7 (-15.1 to -2.3) Moderate confidence in evidence, upgraded for magnitude of effect
	Lamotrigine	2,355	43.5	2 Class II,[18, 42] 3 Class III[15, 21, 56]	3.4 (0.4–9.2)	-11.0 (-17.8 to -4.1) Moderate confidence in evidence, upgraded for magnitude of effect
	Levetiracetam	556	0.0	1 Class II,[18] 1 Class III[56]	3.1 (0.2–9.3)	-11.3 (-18.3 to -4.2) Moderate confidence in evidence, upgraded for magnitude of effect
	Oxcarbazepine	71	0.0	1 Class III[56]	3.5 (3.2 to -30.3)	-10.8 (-25.4 to 3.7) Very low confidence in evidence
	Phenobarbital	384	0.0	1 Class II,[18] 2 Class III[45, 56]	4.1 (0.2–12.9)	-10.2 (-18.5 to -1.9) Moderate confidence in evidence, upgraded for magnitude of effect

	Phenytoin	758	0.0	2 Class II,[18, 42] 2 Class III[45, 56]	2.0 (0.1 to 6.4)	-12.3 (-18.5 to -6.1) Moderate confidence in evidence, upgraded for magnitude of effect
	Primidone	43	NA	1 Class III[45]	10.6 (2.1–62.1)	-3.7 (-34.2 to 26.8) Very low confidence in evidence, one class III study
	Topiramate	359	NA	1 Class II[18]	1.3 (0.2–7.7)	-13.0 (-19.5 to -6.5) Moderate confidence in evidence, upgraded for magnitude of effect
	Valproic acid	3,578	31.9	3 Class II,[18, 23, 31] 5 Class III[21, 45, 49, 51, 56]	14.3 (9.5 to 20.1)	Reference
Cardiac						
	Carbamazepine	5,211	70.8	4 Class II,[10, 18, 42, 44] 6 Class III[21, 35, 45, 49, 51, 56]	8.5 (4.8–13.2)	-33.4 (-52.7 to -14.1) Moderate confidence in evidence, upgraded for magnitude of effect
	Lamotrigine	6,179	87.0	1 Class I,[41] 4 Class II,[10, 18, 25, 42] 5 Class III[14, 15, 21, 35, 56]	16.6 (7.8–28.5)	-25.3 (-46.8 to -3.8) Moderate confidence in evidence, upgraded for magnitude of effect
	Levetiracetam	556	81.3	1 Class II,[18] 1 Class III[56]	12.5 (0.1–53.4)	-29.4 (-62.0 to 3.2) Low confidence in evidence, upgraded for magnitude of effect
	Oxcarbazepine	71	0.0	1 Class III[56]	42.3 (5.4–104.3)	0.4 (-52.6 to 53.3) Very low confidence in evidence
	Phenobarbital	432	0.0	2 Class II,[18, 44] 2 Class III[45, 56]	41.9 (25.1–62.7)	Reference
	Phenytoin	955	6.5	1 Class I,[41] 3 Class II,[18, 42, 44] 2 Class III[45, 56]	19.9 (11.6–30.3)	-22.0 (-43.0 to -1.0) Moderate confidence in evidence, upgraded for magnitude of effect
	Primidone	147	0.0	1 Class II,[44] 2 Class III[45, 51]	11.6 (0.8 to 35.1)	-8.2 (-27.8 to 11.3) Low confidence in evidence, upgraded for magnitude of effect
	Topiramate	359	0.0	1 Class II[18]	2.8 (2.1 to -11.9)	-39.1 (-58.5 to -19.6) High confidence in evidence, upgraded twice for magnitude of effect

	Valproic acid	2,212	66.2	1 Class I,[41] 5 Class II,[10, 18, 23, 31, 44] 6 Class III[21, 35, 45, 49, 51, 56]	25.1 (16.9–35.0)	-16.8 (-37.6 to 4.1) Low confidence in evidence
Oral and cleft palate						
	Carbamazepine	4,103	27.8	3 Class II,[18, 42, 44] 5 Class III[21, 36, 45, 49, 51]	4.7 (2.5–7.6)	-17.6 (-37.0 to 1.8) Low confidence in evidence
	Lamotrigine	8,052	84.4	4 Class II,[17, 18, 25, 42] 4 Class III[14, 16, 21, 36]	4.6 (1.3–9.9)	-17.7 (-37.4 to 2.0) Low confidence in evidence
	Levetiracetam	450	0.0	1 Class II[18]	0.0 (0.0–3.8)	-22.3 (-41.6 to -3.0) High confidence in evidence, upgraded twice for large magnitude of effect
	Phenobarbital	295	14.3	2 Class II,[18, 44] 1 Class III[45]	22.3 (7.1–45.6)	Reference
	Phenytoin	904	0.0	3 Class II,[18, 42, 44] 2 Class III[45, 51]	9.7 (4.4–17.2)	-12.6 (-32.8 to 7.7) Low confidence in evidence
	Primidone	86	0.4	1 Class II,[44] 1 Class III[45]	16.6 (0.6–54.1)	-5.7 (-38.6 to 27.3) Low confidence in evidence
	Topiramate	846	0.0	2 Class II[17, 18]	14.1 (7.3–23.1)	-8.2 (-29.0 to 12.6) Low confidence in evidence
	Valproic acid	3,636	27.8	4 Class II,[18, 23, 31, 44] 5 Class III[21, 36, 45, 49, 51]	8.0 (4.6–12.2)	-14.3 (-34.0 to 5.3) Low confidence in evidence
Urogenital						
	Carbamazepine	1,033	NA	1 Class II[18]	1.4 (0.0–4.6)	-11.0 (-17.2 to -4.8) Moderate confidence in evidence, upgraded for magnitude of effect
	Lamotrigine	3,203	80.3	1 Class II,[18] 2 Class III[14, 15]	2.0 (0.0–8.9)	-10.4 (-17.7 to -3.1) Moderate confidence in evidence, upgraded for magnitude of effect
	Levetiracetam	450	0.0	1 Class II[18]	1.0 (0.2–6.1)	-11.4 (-17.9 to -4.9) High confidence in evidence, upgraded twice for very large magnitude of effect

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	Phenobarbital	199	0.0	1 Class II[18]	7.3 (0.3–23.8)	-5.2 (-18.2 to 7.9) Low confidence in evidence
	Phenytoin	416	0.0	1 Class II[18]	1.1 (0.2–6.6)	-11.3 (-17.9 to -4.8) High confidence in evidence, upgraded twice for very large magnitude of effect
	Topiramate	359	0.0	1 Class II[18]	7.2 (1.1–18.5)	-5.3 (-15.7 to 5.1) Low confidence in evidence
	Valproic acid	1,432	0.0	2 Class II[18, 23]	12.4 (7.4–18.8)	Reference
Renal						
	Carbamazepine	2,841	3.6	1 Class II,[42] 5 Class III[21, 45, 49, 51, 56]	5.5 (3.1–8.7)	-8.2 (-14.5 to -1.9) Moderate confidence in evidence, upgraded for magnitude of effect
	Lamotrigine	2,354	41.9	1 Class II,[42] 3 Class III[14, 21, 56]	6.6 (2.1–13.6)	-7.1 (-15.1 to 0.9) Low confidence in evidence
	Levetiracetam	106	0.0	1 Class III[56]	9.4 (7.3–40.1)	-4.3 (-21.6 to 13.1) Very low confidence in evidence
	Oxcarbazepine	71	0.0	1 Class III[56]	14.1 (10.9–59.5)	0.4 (-24.6 to 24.3) Very low confidence in evidence
	Phenobarbital	185	0.0	2 Class III[54, 56]	2.5 (0.5–14.8)	-11.2 (-20.3 to -2.1) Moderate confidence in evidence, upgraded for magnitude of effect
	Phenytoin	466	0.0	1 Class II,[42] 3 Class III[45, 51, 56]	8.0 (2.0–18.1)	-5.7 (-15.5 to 4.1) Low confidence in evidence
	Primidone	43	0.0	1 Class III[45]	0.0 (0.0–39.6)	-13.7 (-34.3 to 6.9) Very low confidence in evidence
	Valproic acid	1,637	0.0	1 Class II,[42] 5 Class III[21, 45, 49, 51, 56]	13.7 (8.6–19.9)	Reference

MCM = major congenital malformation; ASM = antiseizure medication; RMD = raw mean difference; CI = confidence interval; NA = not applicable; I^2 = a statistical measure of study heterogeneity

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For neural tube defects (NTDs), valproic acid was associated with the highest prevalence (14.3 per 1,000 live births, 95% CI 9.5–20.1). Compared to valproic acid, a lower prevalence of NTDs was seen with exposure to carbamazepine (PD -8.7, 95% CI -15.1 to -2.3), lamotrigine (PD -11.0, 95% CI -17.8 to -4.1), levetiracetam (PD -11.3, 95% CI -18.3 to -4.2), phenobarbital (PD -10.2, 95% CI -18.5 to -1.9), phenytoin (PD -12.3, 95% CI -18.5 to -6.1), and topiramate (PD -13.0, 95% CI -19.5 to -6.5). Compared to valproic acid, no significant difference in prevalence of NTDs was seen for oxcarbazepine or primidone, though fewer exposures were captured for these.

Cardiac malformations were most frequent with oxcarbazepine exposure (42.3 per 1,000 live births, 95% CI 5.4–104.3), though this is based on only 71 exposures from a single Class III study, followed closely by phenobarbital exposure (41.9 per 1,000 live births, 95% CI 25.1–62.7) and by valproic acid (25.2 per 1,000 live births, 95% CI 16.9–35.0). Compared to phenobarbital, a lower prevalence of cardiac malformations per 1,000 live births was seen with exposure to carbamazepine (PD -33.4, 95% CI -52.7 to -14.1), lamotrigine (PD -25.3, 95% CI -46.8 to -3.8), phenytoin (PD -22.0, 95% CI -43.0 to -1.0), and topiramate (PD -39.1, 95% CI 58.5 to -19.6), while not reaching statistical significance with levetiracetam, oxcarbazepine, primidone, and valproic acid.

Phenobarbital was also associated with the highest prevalence of oral clefts per 1,000 live births (22.3 per 1,000 live births, 95% CI 7.1–45.6), followed by topiramate (14.1 per 1,000 live births, 95% CI 7.3–23.1). Compared to phenobarbital, a lower prevalence of oral clefts was seen with exposure to levetiracetam (PD -22.3, 95% CI -41.6 to -3.0), with no significant difference compared to carbamazepine, lamotrigine, phenytoin, primidone, topiramate, and valproic acid. Compared with topiramate, a decrease in oral clefts was seen with exposure to carbamazepine (PD -9.4, 95% CI -17.7 to -1.1), lamotrigine (PD -9.5, 95% CI -18.6 to -0.5), and levetiracetam (PD -14.1, 95% CI -22.3 to -5.9), while no significant difference was seen with phenobarbital, phenytoin, or primidone.

Valproic acid was associated with the highest prevalence of urogenital malformations, including hypospadias, per 1,000 live births (12.4 per 1,000 live births, 95% CI 7.4–18.8). Compared to valproic acid, a lower prevalence of urogenital MCMs was seen after exposure to carbamazepine (PD -11.0, 95% CI -17.2 to -4.8), lamotrigine (PD -10.4, 95% CI -17.7 to -3.1), levetiracetam (PD -11.4, 95% CI -17.9 to -4.9), and phenytoin (PD -11.3, 95% CI -17.9 to -4.8) while not reaching significance for phenobarbital or topiramate. Valproic acid also had a higher prevalence of renal malformations with a prevalence of 13.7 per 1,000 births (95% CI 8.6–19.9) when compared to carbamazepine (PD -8.2, 95% CI -14.5 to -1.9) and phenobarbital (PD -11.2, 95% CI -20.3 to -2.1), while not reaching significance compared to lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, and primidone.

No data were found for specific MCMs for acetazolamide, clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, vigabatrin, and zonisamide.

Conclusions

Prevalence of any MCM with ASM monotherapy: Moderate confidence in evidence

Among children born to PWECP, those exposed to valproic acid in utero likely have a higher prevalence of any MCM per 1,000 births when compared to those exposed to carbamazepine (PD 53, 95% CI 34.1–71.9), clobazam (PD 65.4, 95% CI 16.7–114.2), clonazepam (PD 66.5, 95% CI 31.9–101.1), gabapentin (PD 65.8, 95% CI 26.7–104.9), lamotrigine (PD 66, 95% CI 48.2–83.8), levetiracetam (PD 61.9, 95% CI 37.6–86.2), oxcarbazepine (PD 65.4, 95% CI 45.5–85.3), and topiramate (PD 52.2, 95% CI 29.8–74.6). All comparisons are indirect and were upgraded for large magnitude of effect.

Prevalence of any MCM with ASM monotherapy: Low confidence in evidence

Among children born to PWECP, those exposed to carbamazepine possibly have a higher prevalence of any MCM when compared to those exposed to lamotrigine (indirect comparison).

Children born to PWECP who were exposed to phenobarbital possibly have a higher prevalence of any MCM when compared to those exposed to carbamazepine, lamotrigine, levetiracetam, and oxcarbazepine. No difference was found when comparing phenobarbital exposure to clobazam, clonazepam, gabapentin, phenytoin, primidone, or topiramate exposure (all indirect comparisons).

Among children born to PWECP, those exposed to phenytoin possibly have a higher prevalence of any MCM when compared to those exposed to lamotrigine and oxcarbazepine while no difference was found when compared to carbamazepine, clobazam, clonazepam, gabapentin, levetiracetam, or topiramate (all indirect comparisons).

Children born to PWECP who were exposed to valproic acid possibly have a higher prevalence of any MCM when compared to those exposed to phenobarbital and phenytoin (all indirect comparisons).

Among children born to PWECP, those exposed to clobazam, clonazepam, levetiracetam, oxcarbazepine, or topiramate in utero possibly have no difference in the prevalence of any MCM compared to each other or compared to carbamazepine, gabapentin, phenobarbital, or phenytoin (all indirect comparisons).

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Prevalence of any MCM with ASM monotherapy: Very low confidence in evidence

Among children born to PWECP, there is insufficient evidence to support or refute a difference in the prevalence of MCMs among children exposed to clobazam, primidone, or zonisamide monotherapy in utero compared to those exposed to other ASMs (all indirect comparisons downgraded for statistical imprecision).

There is insufficient evidence on the prevalence of any MCM with in utero exposure to acetazolamide, eslicarbazepine acetate, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, and vigabatrin (no available studies with sufficient exposures).

Prevalence of any MCM with ASM polytherapy vs monotherapy

Among children exposed to ASMs in utero and born to PWECP, there is possibly a lower prevalence of any MCM per 1,000 births with exposure to lamotrigine in monotherapy compared to lamotrigine in polytherapy (low confidence in evidence, all indirect comparisons).

Among children exposed to ASMs in utero and born to PWECP, there is possibly no difference in the prevalence of any MCM with exposure to carbamazepine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, or valproic acid in polytherapy compared to each of these ASMs in monotherapy (low confidence in evidence, all indirect comparisons).

Among children exposed to ASMs in utero and born to PWECP, there is insufficient evidence to support or refute a decrease or no difference in the prevalence of any MCM with exposure to clobazam, clonazepam, ethosuximide, gabapentin, primidone, topiramate, or zonisamide in polytherapy compared to each of these ASMs in monotherapy (very low confidence in evidence, all indirect comparisons downgraded for statistical imprecision).

Prevalence of any MCM with high doses vs low-medium doses of ASMs in monotherapy

Among children exposed to ASMs in utero and born to PWECP, there is insufficient evidence to determine if those exposed to high doses of valproic acid or phenobarbital have a higher prevalence of any MCM per 1,000 live births when compared to those exposed to low-medium doses of these ASMs (very low confidence in evidence, all indirect comparisons downgraded for imprecision and not further upgraded for magnitude of effect).

Among children exposed to ASMs in utero and born to PWECP, there is possibly no difference in the prevalence of any MCM with exposure to high doses of carbamazepine or lamotrigine when compared to exposure to low-medium doses of these ASMs (low confidence in evidence, indirect comparisons).

There is insufficient evidence to support or refute an increase in the prevalence of any MCM with exposure to high doses of phenytoin compared to low-medium doses of phenytoin (very low confidence in evidence, downgraded for imprecision).

Prevalence of specific MCMs with ASM monotherapy: Brain malformations

Among children born to PWECP and exposed to ASMs in utero, there is insufficient evidence to support or refute that exposure to phenytoin monotherapy increases the prevalence of brain malformations per 1,000 live births compared to exposure to carbamazepine, lamotrigine, or valproic acid monotherapy (very low confidence in evidence, indirect comparisons downgraded for lack of statistical precision).

Among children born to PWECP and exposed to ASMs in utero, there is possibly no difference in prevalence of brain malformations per 1,000 births with exposure to valproic acid compared to exposure to carbamazepine, lamotrigine, or phenytoin (low confidence in evidence).

Prevalence of specific MCMs with ASM monotherapy: NTDs

Among children born to PWECP and exposed to ASMs in utero, compared to exposure to valproic acid monotherapy, the prevalence of NTDs per 1,000 live births is likely lower with exposure to carbamazepine (PD -8.7, 95% CI -15.1 to -2.3), lamotrigine (PD -11.0, 95% CI -17.8 to -4.1), levetiracetam (PD -11.3, 95% CI -18.3 to -4.2), phenobarbital (PD -10.2, 95% CI -18.5 to -1.9), phenytoin (PD -12.3, 95% CI -18.5 to -6.1), and topiramate (PD -13.0, 95% CI -19.5 to -6.5) (moderate confidence in evidence, indirect comparisons upgraded for large magnitude of effect).

There is possibly no difference in the prevalence of NTDs with exposure to valproic acid monotherapy compared to exposure to oxcarbazepine, or primidone monotherapy (low confidence in evidence, indirect comparisons).

Prevalence of specific MCMs with ASM monotherapy: Cardiac MCMs

Among children born to PWECP and exposed to ASMs in utero, compared to exposure to phenobarbital monotherapy, the prevalence of cardiac MCMs is highly likely lower with exposure to topiramate (PD -39.1, 95% CI -58.5 to -19.6) monotherapy (high confidence in evidence, indirect comparisons upgraded 2 levels for very large magnitude of effect).

Compared to exposure to phenobarbital monotherapy, the prevalence of cardiac MCMs is likely lower with exposure to carbamazepine (PD -33.4, 95% CI -52.7 to -14.1), lamotrigine (PD -25.3, 95% CI -46.8 to -3.8), and phenytoin (PD -22.0, 95% CI -43.0 to -1.0) monotherapy (moderate confidence in evidence, all indirect comparisons upgraded for large magnitude of effect).

There is possibly no difference in the prevalence of cardiac MCMs with phenobarbital monotherapy exposure compared to levetiracetam, oxcarbazepine, or valproic acid monotherapy exposure (low confidence in evidence, all indirect comparisons not reaching significance), while there is insufficient evidence to support or refute a difference compared to primidone monotherapy exposure (very low confidence in evidence, single Class III study).

Oxcarbazepine had an absolute prevalence of cardiac MCMs that was higher than phenobarbital, but with low precision and a small number of exposures. As a result, phenobarbital was retained as the anchor for any comparisons between ASMs.

Prevalence of specific MCMs with ASM monotherapy: Oral clefts or cleft palates

Among children exposed to ASMs in utero and born to PWECP, compared with exposure to phenobarbital monotherapy, the prevalence of oral clefts or cleft palates is highly likely lower when compared to exposure to levetiracetam monotherapy (PD -22.3, 95% CI -41.6 to -3.0) (high confidence in evidence, indirect comparison upgraded for very large magnitude of effect).

There is possibly no difference in the prevalence of oral clefts or oral palates with phenobarbital exposure compared to carbamazepine, lamotrigine, phenytoin, primidone, topiramate, or valproic acid exposure (low confidence in evidence, indirect comparisons).

Compared with exposure to topiramate monotherapy, the prevalence of oral clefts or cleft palates is highly likely lower with exposure to levetiracetam (PD -14.1, 95% CI -22.3 to -5.9; high confidence in evidence, upgraded for very large magnitude of effect) and is likely lower with exposure to carbamazepine (PD -9.4, 95% CI -17.7 to -1.1) or lamotrigine (PD -9.5, 95% CI -18.6 to -0.5) monotherapy (moderate confidence in evidence, indirect comparisons upgraded for large magnitude of effect).

There is possibly no difference in the prevalence of oral clefts or cleft palates per 1,000 live births with exposure to topiramate monotherapy compared to exposure to phenobarbital, phenytoin, primidone, or valproic acid monotherapy (low confidence in evidence, all indirect comparisons).

Prevalence of specific MCMs with ASM monotherapy: Urogenital MCMs

Among children born to PWECP, compared with exposure to valproic acid monotherapy in utero, the prevalence of urogenital MCMs is highly likely higher with exposure to levetiracetam monotherapy (PD -11.4, 95% CI -17.9 to -4.9) and phenytoin monotherapy (PD -11.3, 95% CI -17.9 to -4.8) (high confidence in evidence, all indirect comparisons upgraded for very large magnitude of effect).

Among children born to PWECP, compared with exposure to valproic acid monotherapy in utero, the prevalence of urogenital MCMs is likely lower with in utero exposure to

carbamazepine monotherapy (PD -11.0, 95% CI -17.2 to -4.8), and lamotrigine monotherapy (PD -10.4, 95% CI -17.7 to -3.1) (moderate confidence in evidence, all indirect comparisons upgraded for large magnitude of effect), and is possibly not different compared with phenobarbital and topiramate monotherapy exposure (low confidence in evidence, all indirect comparisons).

Prevalence of specific MCMs with ASM monotherapy: Renal MCMs

Among children born to PWECP, compared with exposure to valproic acid monotherapy in utero, the prevalence of renal MCMs is likely lower with exposure to carbamazepine (PD -8.2, 95% CI -14.5 to -1.9) and phenobarbital (PD -11.2, 95% CI -20.3 to -2.1) (moderate confidence in evidence, all indirect comparisons upgraded for large magnitude of effect); is possibly not different compared with exposure to lamotrigine, levetiracetam, or phenytoin monotherapy (low confidence in evidence, all indirect comparisons); and there is insufficient evidence to support or refute a difference compared with oxcarbazepine or levetiracetam (very low confidence in evidence).

Prevalence of specific MCMs with ASM monotherapy: ASMs with insufficient evidence

There is insufficient evidence on the prevalence of specific malformations with intrauterine exposure to acetazolamide, clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, lacosamide, nitrazepam, oxcarbazepine, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, vigabatrin, and zonisamide (no available studies).

2. What is the prevalence of adverse perinatal outcomes associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high doses vs low-medium doses of ASMs, in children born to PWECP?

Twenty-four studies[12, 20, 24, 26, 27, 36, 41, 46, 50, 53, 55, 57, 60, 64-74] reported perinatal outcomes (perinatal death, the proportion born SGA, and the proportion born prematurely [<37 weeks of gestation]) in PWECP. Of these, several reported on the same cohort of participants over successive years, and 11[26, 27, 36, 53, 55, 64, 66, 68, 69, 71, 73] were retained for unadjusted prevalence reports. Thirteen studies reported a primary perinatal outcome, of which 8 provided comparisons among PWECP treated with an ASM during pregnancy (2 Class I, 6 Class III).[41, 55, 57, 60, 68, 69, 71, 73]

The prevalence of premature birth in the general population is approximately 10%.[75] Among the included studies, all ASMs had overlapping 95% CIs of the prevalence of premature birth. The author panel used lamotrigine as an anchor for comparisons because it had the highest number of exposures. Among those exposed to any of 12 ASMs in monotherapy (carbamazepine, clobazam, clonazepam, gabapentin, levetiracetam, phenobarbital, phenytoin, primidone, topiramate,

valproic acid, and zonisamide), there was no significant difference in prevalence of premature birth compared to those exposed to lamotrigine (table 5).

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Table 5: Unadjusted prevalence of premature birth by ASM monotherapy

ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence compared to Reference (95% CI)
Carbamazepine	2,005	87.2	1 Class II,[66] 4 Class III[36, 64, 69, 71]	93.1 (55.4–139.4)	-34.2 (-132.9 to 64.2) Low confidence in evidence
Clobazam	30	NA	1 Class III[69]	177.1 (64.6–329.9)	49.7 (-110.2 to 209.5) Very low confidence in evidence
Clonazepam	262	NA	1 Class III[69]	89.7 (58.2–127.2)	-37.7 (-133.3 to 57.9) Very low confidence in evidence
Gabapentin	72	NA	1 Class III[69]	131.4 (64.1–218.2)	4.0 (-113.9 to 121.9) Very low confidence in evidence
Lamotrigine	2,396	96.4	1 Class I,[73] 1 Class II,[66] 5 Class III[36, 64, 68, 69, 71]	127.4 (51.8–230.2)	Reference
Levetiracetam	494	75.2	1 Class I,[73] 2 Class III[27, 53]	81.0 (33.3–147.2)	-46.4 (-152.2 to 59.4) Low confidence in evidence
Oxcarbazepine	837	42.3	2 Class III[64, 69]	53.1 (34.5–75.4)	-74.3 (-165.8 to 17.2) Low confidence in evidence
Phenobarbital	96	NA	1 Class III[69]	109.1 (55.1–178.6)	-18.3 (-126.8 to 90.1) Very low confidence in evidence
Phenytoin	81	0.0	2 Class III[64, 71]	107.8 (50.4–183.6)	-19.6 (-130.9 to 91.7) Low confidence in evidence
Primidone	20	NA	1 Class III[69]	166.0 (40.7–352.9)	38.5 (-141.2 to 218.3) Low confidence in evidence
Topiramate	406	0.0	2 Class III[68, 69]	102.9 (75.3–134.2)	-24.6 (-118.5 to 69.3) Low confidence in evidence
Valproic acid	1,568	23.2	1 Class II,[66] 6 Class III[26, 36, 53, 64, 69, 71]	70.7 (55.6–87.6)	-56.7 (-147.3 to 33.9) Low confidence in evidence
Zonisamide	98	NA	1 Class III[76]	106.0 (53.3–174.1)	-21.4 (-129.1 to 86.3) Very low confidence in evidence

ASM = antiseizure medication; CI = confidence interval; NA = not applicable; I^2 = a statistical measure of study heterogeneity

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The unadjusted prevalence of children born SGA per 1,000 live births across monotherapy with 13 ASMs is shown in table 6. Prevalence differences are shown using topiramate as the reference because it has been commonly associated with children born SGA in prior literature.

There was no significant difference in the prevalence of children born SGA between those exposed to topiramate monotherapy and those exposed to carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, valproic acid, or zonisamide monotherapy (all indirect comparisons).

No data were found for the prevalence of prematurity or children born SGA among children of PWECP exposed to acetazolamide, eslicarbazepine acetate, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, or tiagabine.

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Table 6: Unadjusted prevalence of SGA by ASM monotherapy

ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence compared to reference (95% CI)
Carbamazepine	3,033	96.3	1 Class II,[67] 5 Class III[36, 64, 69, 71, 74]	75.7 (31.3–137.5)	-4.4 (-153.9 to 145.0) Low confidence in evidence
Clobazam	30	0.0	1 Class III[69]	177.1 (64.6–329.9)	96.9 (-95.7 to 289.6) Very low confidence in evidence
Clonazepam	276	NA	2 Class III[69]	165.4 (123.0–212.7)	85.2 (-61.5 to 231.9) Low confidence in evidence
Gabapentin	225	91.3	2 Class III[69, 74]	58.5 (0.1–214.2)	-21.7 (-197.7 to -154.3) Low confidence in evidence
Lamotrigine	2,597	98.0	1 Class I,[73] 1 Class II,[67] 5 Class III[36, 64, 69, 71, 74]	85.1 (13.6–209.6)	5.0 (-165.7 to 175.6) Low confidence in evidence
Levetiracetam	835	85.2	1 Class I,[73] 2 Class III[69, 74]	52.9 (6.8–138.6)	-27.3 (-181.7 to 127.1) Low confidence in evidence
Oxcarbazepine	1,045	96.1	3 Class III[64, 69, 74]	58.0 (6.8–154.2)	-22.2 (-180.1 to 135.7) Low confidence in evidence
Phenobarbital	274	95.3	2 Class III[69, 74]	89.3 (0.3–310.0)	9.1 (-199.4 to 217.6) Low confidence in evidence
Phenytoin	464	24.5	3 Class III[64, 71, 74]	14.4 (2.7–35.1)	-65.8 (-206.3 to 74.8) Low confidence in evidence
Primidone	20	0.0	1 Class III[69]	166.0 (40.7–352.9)	85.8 (-123.6 to 295.2) Very low confidence in evidence
Topiramate	453	93.6	2 Class III[69, 74]	80.2 (0.3–279.6)	Reference
Valproic acid	1,829	97.6	1 Class II,[67] 7 Class III[26, 36, 64, 69, 71, 74]	147.1 (53.9–276.0)	66.9 (-111.5 to 245.4) Low confidence in evidence
Zonisamide	125	NA	1 Class III[74]	20.4 (3.1–52.4)	-59.7 (-201.6 to 82.1) Low confidence in evidence

SGA = small for gestational age; ASM = antiseizure medication; CI = confidence interval; NA = not applicable; I^2 = a statistical measure of study heterogeneity

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The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study (Class I) included 323 pregnancies between 1999 and 2004.[41] Fetal deaths included spontaneous abortions and stillbirth. Eight fetal deaths occurred, with no significant difference across ASM exposures ($p \geq 0.20$). A second Class III study of this same NEAD pregnancy cohort reported the prevalence of children born SGA, which was defined as a birth weight at or below the tenth percentile for gestational age and sex.[71] After adjusting for tobacco use, gestational diabetes, and gestational age, the odds of children being born SGA was higher with valproic acid monotherapy than with phenytoin (OR 7.25, 95% CI 1.30–40.28) or lamotrigine monotherapy (OR 4.08, 95% CI 1.11–14.96), and higher with carbamazepine monotherapy compared to phenytoin monotherapy (OR 5.58, 95% CI 1.06–29.34). The comparisons of valproic acid to carbamazepine and carbamazepine to lamotrigine did not reveal statistically significant differences.

The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study (Class I) examined 345 infants born to 331 pregnant people with epilepsy and 106 infants born to 102 healthy pregnant people.[73] Topiramate was associated with the lowest birth weight z scores (mean -1.23, SD 0.32) and lamotrigine was associated with the highest (mean 0.15, SD 0.77) compared to other ASMs (standard mean difference -1.4, 95% CI -2.24 to -0.39). Comparisons for prematurity found no evidence of any difference when the same ASMs were compared to lamotrigine ($p = 0.34$) after adjusting for periconceptual folate use, alcohol use during pregnancy, and the child's race.

An analysis of the North American Antiepileptic Drug Pregnancy Registry (Class III study) that reported births among PWECP that occurred between 1997 and 2016 demonstrated an increased risk of children being born SGA with intrauterine exposure to topiramate, phenobarbital, and zonisamide monotherapies, as compared to exposure to lamotrigine (aRR 2.4, 95% CI 1.8–3.1; aRR 2.4, 95% CI 1.6–3.6; and aRR 1.9, 95% CI 1.2–3.0 respectively).[74] Comparisons of all other ASMs (i.e., phenytoin, gabapentin, carbamazepine, levetiracetam, oxcarbazepine, and valproic acid) with lamotrigine and their risks of children born SGA were not statistically significant. A dose effect was noted for topiramate, with a prevalence of children born SGA of 8.5% among those exposed to mean topiramate doses <50 mg/d and 19.9% for those exposed to higher doses ($p = 0.04$). There was no observed dose effect for lamotrigine, zonisamide, or phenobarbital.

EURAP reported data (Class I) on intrauterine deaths among PWECP treated with an ASM during pregnancies occurring from 1999–2013.[60] The investigators defined intrauterine deaths as including fetal loss (occurring before 24 gestational weeks) and stillbirths (occurring after 24 gestational weeks). Among 7,055 pregnancies, using a multivariable random-effects log-binomial model to adjust for 11 covariates (including maternal age and prior history of intrauterine deaths), there was no difference in the risk of intrauterine death among individual ASM monotherapies when compared to valproic acid (lamotrigine RR 0.851, 95% CI 0.658–1.101; carbamazepine RR 0.904, 95% CI 0.688–1.189; levetiracetam RR 0.888, 95% CI 0.589–1.337; oxcarbazepine RR 0.804, 95% CI 0.505–1.280; and phenobarbital RR 0.839, 95% CI

0.531–1.326). There was an increased risk of intrauterine death with ASM polytherapy as compared to monotherapy (RR 1.38, 95% CI 1.14–1.66).

The Danish Medical Birth Registry reported on approximately 2,200 births of children exposed to ASMs in utero among PWECP from 1997–2008 (Class III).[69] The investigators did not compare the risk of intrauterine death between different ASMs in monotherapy. Use of ASMs in polytherapy vs monotherapy did not increase the risk of being born prematurely, but it did increase the risk of being born SGA (RR 1.21, 95% CI 1.08–1.35). The risk of preterm birth or being born SGA was not evidently different between individuals exposed to high doses vs low-medium doses of ASMs.

The Australian Register reported on intrauterine death as a combined endpoint of spontaneous abortions and stillbirths from 1,367 pregnancies with fetal exposure to an ASM in monotherapy and 527 with fetal exposure to ASMs in polytherapy (Class III study).[57] There was no statistical evidence of a difference between polytherapy and monotherapy exposure (RR 1.22, 95% CI 0.75–1.98). The investigators did not compare the risk of intrauterine death between different ASMs in monotherapy.

Conclusions

Among children exposed to ASMs in utero and born to PWECP, the prevalence of intrauterine death is highly likely not different across carbamazepine, lamotrigine, and valproic acid when used in monotherapy (high confidence in evidence, 2 Class I studies) and likely not different for phenobarbital, oxcarbazepine, and phenytoin (moderate confidence in evidence, 1 Class I study).

Among children exposed to ASMs in utero and born to PWECP, the prevalence of intrauterine death is likely higher with polytherapy exposure compared to monotherapy exposure (RR 1.38, 95% CI 1.14–1.66) (moderate confidence in evidence, 1 Class I study); and there is likely no dose effect for lamotrigine, carbamazepine, and valproic acid (moderate confidence in evidence, 1 Class I study).

Among children born to PWECP, there is possibly no difference in the prevalence of premature birth with intrauterine exposure to different ASMs in monotherapy, including carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, vigabatrin, and zonisamide (low confidence in evidence, 1 Class III study, p=0.34, and all indirect comparisons) There is insufficient evidence to support or refute a difference in prevalence of premature birth with in utero exposure to clobazam, clonazepam, gabapentin, or zonisamide compared to lamotrigine, and no dose effect across ASMs or between ASMs used in monotherapy and polytherapy (very low confidence in evidence, 1 Class III study).

Among children exposed to ASMs in utero and born to PWECP, there is possibly a higher risk of being born SGA after exposure to valproic acid as compared to lamotrigine, and after exposure to topiramate as compared to lamotrigine (2 Class III studies, low confidence in evidence).

Among children exposed to ASMs in utero and born to PWECP, there is possibly no difference in risk of being born SGA when exposed to carbamazepine compared to lamotrigine (low confidence in the evidence, 2 Class III studies).

Among children exposed to ASMs in utero and born to PWECP, there is possibly no difference in risk of being born SGA with exposure to topiramate compared to carbamazepine, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, and valproic acid (low confidence in evidence, indirect comparisons).

There is insufficient evidence to support or refute a higher risk of being born SGA after in utero exposure to valproic acid as compared to phenytoin or carbamazepine, as well as after exposure to carbamazepine as compared to phenytoin (very low confidence in evidence, 1 Class III study). There is insufficient evidence to support an increased risk of being born SGA after in utero exposure to levetiracetam compared to lamotrigine (very low confidence, 2 Class III studies downgraded for lack of consistency). There is insufficient evidence to support or refute a lower risk of being born SGA after in utero exposure to lamotrigine compared to zonisamide and phenobarbital (very low confidence in evidence, 1 Class III study). There is insufficient evidence to support a lower prevalence of being born SGA after exposure to ASMs in monotherapy compared to exposure to ASMs in polytherapy (very low confidence in evidence, 1 Class III study). There is insufficient evidence to support a dose effect for topiramate, lamotrigine, phenobarbital, and zonisamide (very low confidence in evidence, 1 Class III study).

3. What is the prevalence of adverse neurodevelopmental outcomes associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high vs low-medium doses of ASMs, in children born to PWECP?

We identified 7 studies evaluating IQ (mean age range across studies 6–9.5 years, 2 Class I, 5 Class III)[65, 77-82] and 6 studies evaluating risk of ASD (1 Class II, 5 Class III) among children exposed to ASMs in utero and born to PWECP.[82-84] The unadjusted mean (95% CI) global IQ by ASM monotherapy pooled across these 7 studies is outlined in table 7, and pooled mean unadjusted verbal and non-verbal IQs are outlined in table 8. Mean global, verbal, and nonverbal IQ scores were overall very similar to the general population. Intrauterine exposure to valproic acid was associated with the lowest global IQ (mean 92.7 points, 95% CI 89.1–96.3) and with the lowest verbal IQ (mean 92.1 points, 95% CI 86.9–97.4), while intrauterine exposure to levetiracetam was associated with the lowest nonverbal IQ (mean 99.6 points, 95% CI 95.5–103.7). Compared to valproic acid, children with intrauterine exposure to lamotrigine had

significantly higher mean global IQ scores (RMD 12.9, 95% CI 8.3–17.5). Children with intrauterine exposure to carbamazepine, levetiracetam, or topiramate also had higher mean global IQ scores than those exposed to valproic acid (table 7). The difference in mean global IQ with in utero exposure to phenytoin compared to valproic acid was not statistically significant. Compared to valproic acid, children with intrauterine exposure to lamotrigine (RMD 10.3 points, 95% CI 2.4–18.2) or phenytoin (RMD 10.9 points, 95% CI 2.0–19.8), had significantly higher verbal IQ scores. Children with exposure to levetiracetam, phenytoin, or topiramate also had higher mean verbal IQ scores (table 8). Differences in verbal IQ scores did not reach statistical significance for children with in utero exposure to carbamazepine compared to valproic acid. Compared to valproic acid, children with in utero exposure to carbamazepine or phenytoin had higher mean nonverbal IQ scores (table 8). Differences in nonverbal IQ scores did not reach statistical significance among children exposed to lamotrigine, levetiracetam, or topiramate compared to valproic acid.

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Table 7. Global IQ with exposure to ASM monotherapy

ASM	Total sample size	I^2	Included studies	Global IQ mean (95% CI)	RMD compared to reference (95% CI)
Carbamazepine	316	86.0	2 Class I,[78, 79] 4 Class III[65, 80-82]	100.4 (95.8–105.1)	6.53 (0.39–12.67) Low confidence in evidence
Lamotrigine	129	77.0	1 Class I,[78] 1 Class III[65]	105.8 (100.9–110.6)	11.85 (5.53–18.15) Moderate confidence in evidence, upgraded for magnitude of effect
Levetiracetam	42	NA	1 Class III[77]	99.0 (95.0–103.0)	6.3 (0.9–11.7) Very Low confidence in evidence
Phenytoin	76	84.8	1 Class I,[78] 1 Class III[80]	103.2 (93.0–113.4)	9.29 (-1.63 to 20.21) Very low confidence in evidence, downgraded for imprecision
Topiramate	27	NA	1 Class III[77]	100.5 (95.8–105.2)	6.58 (0.37–12.80) Very low confidence in evidence
Valproic acid	173	69.0	2 Class I,[78, 79] 2 Class III[80, 85]	93.9 (89.1–97.9)	Reference

IQ = intelligence quotient; ASM = antiseizure medication; CI = confidence interval; NA = not applicable; RMD = raw mean difference; I^2 = a statistical measure of study heterogeneity

eAppendix 1. Complete Guideline

Table 8. Verbal and non-verbal IQ with exposure to ASM monotherapy

ASM	Total sample size	I^2	Included studies	Mean verbal or non-verbal IQ (95% CI)	RMD compared to reference (95% CI)
Verbal IQ					
Carbamazepine	283	82.0	2 Class I,[78, 79] 3 Class III[65, 80, 82]	98.4 (94.6–102.2)	6.3 (-0.2 to 12.8) Low confidence in evidence
Lamotrigine	103	79.0	1 Class I,[78] 1 Class III[65]	102.4 (96.5–108.2)	10.3 (2.4–18.2) Moderate confidence in evidence*
Levetiracetam	42	NA	1 Class III[77]	101.0 (97.7–104.3)	8.9 (2.7–15.1) Very Low confidence in evidence
Phenytoin	61	69.2	1 Class I,[78] 1 Class III[80]	103.0 (95.8–110.2)	10.9 (2.0–19.8) Moderate confidence in evidence*
Topiramate	27	NA	1 Class III[77]	99.2 (95.2–103.2)	7.1 (0.5–13.7) Very low confidence in evidence
Valproic acid	160	83.0	2 Class I,[78, 79] 2 Class III[77, 80]	92.1 (86.9–97.4)	Reference
Non-Verbal IQ					
Carbamazepine	197	53.9	1 Class I,[78] 2 Class III[65, 82]	104.7 (102.2–107.3)	3.6 (0.0–7.1) Low confidence in evidence
Lamotrigine	103	75.5	1 Class I,[78] 1 Class III[65]	105.8 (100.9–110.7)	4.6 (-0.8 to 10.1) Low confidence in evidence
Levetiracetam	42	NA	1 Class III[77]	99.6 (95.5–103.7)	-1.6 (-6.3 to 3.2) Very low confidence in evidence
Phenytoin	40	NA	1 Class I[78]	106.0 (103.1–109.0)	4.8 (0.1–8.7)

					Low confidence in evidence
Topiramate	27	NA	1 Class III[85]	102.4 (97.1–107.7)	1.2 (-4.6 to 7.1) Very low confidence in evidence
Valproic acid	96	0.0	1 Class I,[78] 1 Class III[77]	101.2 (98.7–103.6)	Reference

IQ = intelligence quotient; ASM = antiseizure medication; CI = confidence interval; RMD = raw mean difference; NA = not applicable; I^2 = a statistical measure of study heterogeneity

IQ data were not available for acetazolamide, clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, gabapentin, lacosamide, nitrazepam, oxcarbazepine, perampanel, piracetam, pregabalin, primidone, rufinamide, stiripentol, tiagabine, vigabatrin, or zonisamide.

Three studies examined measures of global IQ among children with intrauterine exposure to polytherapy that included valproic acid (1 Class I, 2 Class III). Of these, only 1 Class III study reported on greater than 20 exposed infants and it found a mean global IQ in children of 86.8 points (95% CI 81.2–92.4), not reaching statistical significance compared to monotherapy (RMD 5.93, 95% CI -0.73 to 12.59).

There were no studies directly comparing risk of ASD across exposure to ASMs in children born to PWECP. We identified 6 studies (1 Class II, 5 Class III studies)[83-88] that included data from which an unadjusted prevalence of ASD or a high risk of ASD in association with exposure to specific ASMs could be extracted (table 9). The pooled unadjusted mean (95% CI) prevalence of ASD or ASD traits is highest with intrauterine valproic acid exposure (41.9 per 1,000 live births, 95% CI 32.7–52.3). The 95% CI of the estimates for carbamazepine, clonazepam, lamotrigine, and oxcarbazepine all overlap with the prevalence of ASD in the general population (1.47%).[89] Compared to valproic acid, the prevalence of ASD or risk of ASD was lower with carbamazepine, lamotrigine, or levetiracetam exposure. This difference did not reach statistical significance for children exposed to oxcarbazepine (PD -18.6, 95% CI -37.8 to 0.5).

Table 9. Unadjusted prevalence of ASD, PDD, or ASD traits by ASM monotherapy

ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 of ASD/ASD risk (95% CI)	Difference in prevalence compared to reference (95% CI)
Carbamazepine	4,493	84.9	1 Class II,[83] 4 Class III[84-87]	17.1 (6.2–33.1)	-24.9 (-41.5 to -8.2) Moderate confidence, upgraded for large magnitude of effect
Clonazepam	587	51.7	1 Class II,[83] 1 Class III[86]	20.8 (7.5–40.7)	-21.1 (-40.4 to -1.8) Moderate confidence in evidence, upgraded for large magnitude of effect
Lamotrigine	7,568	66.5	1 Class II,[83] 5 Class III[77, 84, 86, 87]	14.5 (8.6–22.2)	-27.4 (-39.3 to -15.6) Moderate confidence in evidence, upgraded for large magnitude of effect
Levetiracetam	1,226	56.0	2 Class III[86, 88]	11.3 (2.9–25.1)	-30.6 (-45.4 to -15.8) Moderate confidence in evidence, upgraded for large magnitude of effect
Oxcarbazepine	321	NA	1 Class II[83]	23.3 (9.7–42.6)	-18.6 (-37.8 to 0.5) Low confidence in evidence

Valproic acid	3,399	36.7	1 Class II,[83] 4 Class III[85-88]	41.9 (32.7–52.3)	Reference

ASD = autism spectrum disorder; PDD = pervasive developmental disorders; ASM = antiseizure medication; CI = confidence interval; NA = not applicable; I^2 = a statistical measure of study heterogeneity

A Class II population-based study including children born from 1996–2006 evaluated the prevalence of ASD among offspring of PWECP exposed to valproic acid.[83] The birth parent's exposure to ASMs, the diagnosis of ASD in the offspring (defined as autism spectrum disorder using *ICD-10* codes F84.0, F84.1, F84.5, F84.8, and F84.9) and with childhood autism (defined by using *ICD-10* code F84.0), and multiple covariates were identified using a series of Danish administrative databases and ICD codes. Among 6,584 children born to PWECP (432 exposed to valproic acid) with a median follow-up period of 14 years, exposure to valproic acid was associated with an adjusted hazard ratio (aHR) of 1.7 (95% CI 0.9–3.2) for ASD and 2.9 (95% CI 1.4–6.0) for childhood autism, as compared to children born to PWECP exposed to no ASMs or to other ASMs including carbamazepine, clonazepam, lamotrigine, and oxcarbazepine. These estimates were adjusted for parental age at conception, parental psychiatric history, gestational age, birth weight, offspring sex, congenital malformations, and parity. There was no significant difference in ASD (amongst all participants, including those without epilepsy) between valproic acid exposure in the first trimester and exposure later in the pregnancy (aHR 2.9, 95% CI 1.6–5.1 and aHR 3.1, 95% CI 0.8–12.2, respectively), between exposure as monotherapy or polytherapy (aHR 3.0, 95% CI 1.7–5.4 and aHR 1.9, 95% CI 0.5–7.7, respectively), or between exposure in low-medium vs high (>750 mg/d) doses (aHR 3.2, 95% CI 1.7–6.2 and HR 2.5, 95% CI 1.0–6.1, respectively).

An analysis of Swedish administrative data included 14,614 children born to PWECP between 1996 and 2011 and reported on the risk of an ASD diagnosis during follow-up until 2013 (Class III).[87] After adjusting for a list of confounders using Cox proportional hazards models, the authors reported that use of valproic acid was associated with an increased instantaneous risk of ASD as compared to use of lamotrigine (aHR 1.62, 95% CI 0.92–2.85). Confounders included in the regression model were parental age, highest education, co-habitation status, country of origin, prior diagnosis of bipolar affective disorder or schizophrenia, suicide attempts, substance abuse, criminal convictions, in-patient diagnosis of seizures during the preceding 1 year, child's year of birth and birth order, child's sex, smoking during the pregnancy by the pregnant person, and any prior use of psychotropic medications.

One hundred and sixty-one children aged 6–7 years were recruited from the Dutch component of the EURAP database and their IQs were assessed (Class III).[90] After adjusting for maternal IQ and ASM dose (unclear but likely multilinear regression), verbal IQ for children with gestational exposure to valproic acid was, on average, 10.3 points lower (95% CI 3.4–17.3) compared to gestational exposure to lamotrigine, was 9.1 points lower (95% CI 1.3–170) compared to carbamazepine, and was 13.4 points lower (95% CI 5.2–21.6) compared to levetiracetam.

We found no studies reporting risk of autism or ASD with intrauterine exposure to acetazolamide, clobazam, eslicarbazepine acetate, ethosuximide, gabapentin, lacosamide, nitrazepam, perampanel, phenytoin, piracetam, pregabalin, primidone, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin, or zonisamide.

Conclusions

Prevalence of adverse neurodevelopmental outcomes: IQ scores

School age children of PWECP exposed to lamotrigine monotherapy in utero likely have a higher global IQ than children exposed to valproic acid monotherapy in utero (RMD 11.85, 95% CI 5.53–18.15; moderate confidence in evidence, indirect comparisons upgraded for large magnitude of effect).

Children exposed to carbamazepine in utero possibly have a higher global IQ than those exposed to valproic acid (RMD 6.53, 95% CI 0.39–12.67; low confidence in evidence, indirect comparisons).

There is insufficient evidence to support or refute a difference in global IQ among children exposed to levetiracetam, phenytoin, or topiramate compared to those exposed to valproic acid (low confidence in evidence, indirect comparisons of a single study or downgraded for lack of precision).

School age children of PWECP exposed to valproic acid polytherapy in utero possibly have no difference in global IQ compared to children exposed to valproic acid monotherapy (RMD 3.8, 95% CI -6.4 to 14.0; very low confidence in evidence, indirect comparison downgraded for lack of precision).

School age children of PWECP exposed to lamotrigine or phenytoin monotherapy in utero likely have a higher verbal IQ compared to those exposed to valproic acid monotherapy (RMD 10.3, 95% CI 2.4–18.2 and RMD 10.9, 95% CI 2.0–19.8, respectively; moderate confidence in evidence, indirect comparisons upgraded for magnitude of effect).

Children exposed to carbamazepine monotherapy in utero possibly have no difference in verbal IQ compared to those exposed to valproic acid (low confidence in evidence, indirect comparisons).

There is insufficient evidence to support or refute a difference in verbal IQ between children exposed to levetiracetam or topiramate in utero compared to those exposed to valproic acid in utero (very low confidence in evidence, indirect comparison on a single Class III study).

School age children of PWECP exposed to carbamazepine or phenytoin monotherapy in utero possibly have a higher non-verbal IQ compared to those exposed to valproic acid in utero (RMD 3.6, 95% CI 0.0–7.1 and RMD 4.8, 95% CI 0.1–8.7, respectively; low confidence in evidence, indirect comparisons).

Children exposed to lamotrigine in utero possibly have similar non-verbal IQs compared to those exposed to valproic acid in utero (RMD 4.6, 95% CI -0.8 to 10.1, not reaching significance; low confidence in evidence, indirect comparison).

There is insufficient evidence to support or refute a difference in non-verbal IQ with exposure to levetiracetam or topiramate compared to exposure to valproic acid (very low confidence in evidence, indirect comparison on a single Class III study).

There is insufficient evidence on all IQ outcomes with exposure to acetazolamide, clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, lacosamide, nitrazepam, oxcarbazepine, perampanel, piracetam, pregabalin, primidone, rufinamide, stiripentol, tiagabine, vigabatrin, or zonisamide (no available studies).

Prevalence of adverse neurodevelopmental outcomes: ASD and ASD risk

There is likely a lower prevalence of ASD or ASD risk among children exposed in utero to carbamazepine (RMD 24.9, -41.5 to -8.2), clonazepam (RMD -21.1, -40.4 to -1.8), lamotrigine (RMD -27.4, -39.3 to -15.6), or levetiracetam (RMD -30.6, -45.4 to -15.8) in monotherapy compared to those exposed to valproic acid monotherapy (moderate confidence in evidence, indirect comparisons upgraded for magnitude of effect).

There is possibly no difference in the prevalence of ASD or ASD risk among children with in utero exposure to oxcarbazepine compared to those exposed to valproic acid (RMD -18.6, 95% CI -37.8 to 0.5, not reaching significance; low confidence in evidence).

There is possibly no difference in ASD risk when comparing children exposed to valproic acid during the first trimester vs later in pregnancy (aHR 2.9, 95% CI 1.6–5.1 and aHR 3.1, 95% CI, 0.8-12.2, respectively), when comparing children exposed to low-medium doses vs high doses of valproic acid (HR 3.2, 95% CI 1.7–6.2 and HR 2.5, 95% CI 1.0–6.1, respectively), and when comparing valproic acid exposure in monotherapy vs polytherapy (aHR 3.0, 95% CI 1.7–5.4 and aHR 1.9, 95% CI 0.5–7.7, respectively) (low confidence in evidence, 1 Class II study).

There is possibly no difference in ASD risk when comparing exposure to carbamazepine, clonazepam, lamotrigine, and oxcarbazepine in low-medium doses vs high doses (low

confidence in evidence, 1 Class II study) and is possibly no difference in ASD risk with exposure to clonazepam, lamotrigine, or oxcarbazepine monotherapy vs polytherapy (low confidence in evidence, 1 Class II study).

There is insufficient evidence to determine whether toddlers of PWECP exposed to lamotrigine and valproic acid in utero are at increased risk of showing autistic traits (very low confidence in evidence, 1 Class III study).

There is insufficient evidence on the risk of ASD with exposure to acetazolamide, clobazam, eslicarbazepine acetate, ethosuximide, lacosamide, nitrazepam, perampanel, phenobarbital, piracetam, pregabalin, primidone, rufinamide, stiripentol, tiagabine, vigabatrin, or zonisamide (no available studies).

4. What is the effect of intrauterine exposure to folic acid on the prevalence of MCMs, adverse perinatal outcomes, and neurodevelopmental outcomes, and how does this vary by folic acid dose in children born to PWECP treated with ASMs?

There were 9 studies (reporting data from 4 registries)[12, 22, 28, 29, 47, 52, 57, 91, 92] examining folic acid exposure and the prevalence of MCMs in children born to PWECP. EURAP (Class I) examined the prevalence of MCMs among 7,355 pregnancies, 38% of which were in participants taking at least 0.4 mg of folic acid daily from 3 months prior to conception through the first trimester (referred to as appropriate exposure). The adjusted OR of MCMs with appropriate folic acid supplementation was not significant, as compared to those who had not received appropriate folic acid supplementation (OR 1.25, 95% CI 0.99–1.60). Data from the UK and Ireland Epilepsy and Pregnancy Register, a Class II study that reported on 5,206 pregnancies and 3 ASMs, where approximately 50% of PWECP were exposed to preconception folic acid supplementation, did not identify a statistically significant effect of folic acid on the prevalence of MCMs. The Kerala Register in southern India, a Class III study considering 1,622 pregnancies and 8 ASMs, did not identify a benefit of folic acid.[28] The Australian Pregnancy Register, a Class III study of 1,972 pregnancies and 20 ASMs, did not identify a difference in prevalence of MCMs between those with preconception folic acid as compared to those without (OR 1.02, 95% CI 0.69–1.55).[52] An updated analysis of the Australian Pregnancy Register, a Class III study, demonstrated that the risk of fetal malformations was not statistically different between low and high doses of folic acid, although this study lacked statistical precision (i.e., the 95% CI is very wide).[92]

There were 5 studies (reporting data from 3 registries)[78, 93-96] examining folic acid exposure and the prevalence of autistic traits and cognitive outcomes in children born to PWECP, with 2 reporting data from the same registry. The Norwegian Mother and Child Cohort Study, a Class II study of 199 children exposed to 1 of 7 ASMs in utero, found that the odds of autistic traits were significantly increased among those without vs with folic acid supplementation evaluated at 18 months of age (adjusted OR 5.9, 95% CI 2.2–15.8) and at 36 months of age (adjusted OR 7.9,

95% CI 2.5–24.9).[93] The same study reported a statistically significant inverse relation between the birth parent's plasma folic acid concentration (collected during gestational weeks 17–19) and Social Communication Questionnaire scores at 36 months, with a lower plasma concentration associated with greater autistic traits (β = −0.3; p = 0.03).[93] A Class III study of 121 children born to PWECP followed in the Australian Pregnancy Register did not identify a statistically significant association between folic acid dose and the Autism Spectrum Quotient score (β = −0.001, 95% CI -0.004 to 0.002).[96] The NEAD study, a Class I study of 305 PWECP who had 311 live births, demonstrated that periconception folic acid use was associated with an increase in the global IQ of children aged 6 years born to PWECP (RMD 6.0, 95% CI 2.4–9.6).[94] These findings were similar for all 4 ASM monotherapies studied (valproic acid, phenytoin, lamotrigine, and carbamazepine), and were similar for non-verbal index scores (RMD 3.0, 95% CI 0.2–5.8), but did not reach significance for verbal index scores (RMD 3.0, 95% CI -0.2 to 6.2).[94] Of the 127 PWECP taking periconceptional folic acid, only 6 were taking doses of 0.4 mg/d or less. A subsequent analysis, a Class III study, of the NEAD data showed that exposure to greater levels of folic acid from food and supplements was associated with statistically significant increases in IQ at age 6 years. This association between folic acid levels and IQ was not seen among PWECP who only received dietary folic acid and did not receive periconceptional folic acid supplements.

Conclusions

Preconception folic acid supplementation among PWECP taking an ASM likely does not reduce the prevalence of MCMs in their newborn children (OR 1.25, 95% CI 0.99–1.60; moderate confidence in evidence, 1 Class I study).

In toddlers of PWECP exposed to ASM in utero, lack of preconception folic acid supplementation is associated with increased odds of autistic traits at 36 months (adjusted OR 7.9, 95% CI 2.5–24.9); and the birth parent's plasma folic acid levels between 17–19 weeks of gestation is inversely related to the offspring's Social Communication Questionnaire scores at 36 months (β = −0.3; p = 0.03; low confidence in evidence, 1 Class II study).

In school aged children of PWECP exposed to ASMs in utero, preconception folic acid supplementation likely improves global IQ (RMD 6.0, 95% CI 2.4–9.6; moderate confidence in evidence, 1 Class I study).

There is insufficient evidence to determine the effects of folic acid dose on the prevalence of MCMs (very low confidence, 1 Class III study), on full scale IQ (very low confidence, 1 Class III study), or on Autism Spectrum Quotient score (very low confidence, 1 Class III study).[96] There is insufficient evidence to determine the effect of timing of exposure on these outcomes.

PUTTING THE EVIDENCE INTO CLINICAL CONTEXT

eAppendix 1. Complete Guideline

The goal of this guideline is to assist clinicians (e.g., physicians, nurses, and advanced practice providers) in the pharmacological management of PWECP to limit risk of adverse congenital, perinatal, and neurodevelopmental outcomes. Given the breadth of variables that may confound the observed outcomes we examined in this guideline (e.g., genetic conditions, pregnancy conditions, and socioeconomic contexts), we weighted evidence more strongly where analyses could be adjusted for these and other potential confounds (i.e., Class I studies). Demonstration of a dose effect can further support a causal relationship between an exposure and outcome. Although our pre-planned analyses using external comparisons could not reach a level of evidence sufficient to drive recommendations, a statistically and clinically important difference in prevalence of MCMs was found for valproic acid and phenobarbital between high- and low-dose exposures. The only Class I study addressing this question from EURAP demonstrated a dose effect for carbamazepine, lamotrigine, phenobarbital, and valproic acid.[29] To reduce the risk of MCMs, it is reasonable practice to use the lowest appropriate dose of ASMs in PWECP, if clinically feasible.

The available evidence on the association between in utero ASM exposure and neurodevelopmental outcomes is rapidly expanding. Although valproic acid exposure shows a strong effect, caution in counseling with exposure to other ASMs with insufficient data from our preplanned analyses is warranted. While we could not extract sufficient data on topiramate exposure, the SCAN-AED study[86] found even higher prevalences of ASD and intellectual disability with exposure to topiramate than valproic acid. Their adjusted hazard ratios, however, used the prevalence in the general population of children as a comparator group (aHRs for ASD and intellectual disability after topiramate exposure were 2.8 [95% CI 1.4–5.7] and 3.5 [95% CI 1.4–8.6] respectively). Further studies are needed to replicate these findings and examine these outcomes across other ASMs.

Folic acid prescribing practices for PWECP are variable.[97, 98] One much-anticipated outcome from the current systematic review was clarification of the optimal folic acid dose recommended to reduce potential negative effects of ASMs in pregnancy. As discussed, the data do not find that folic acid supplementation reduces the risk of MCMs among PWECP. However, improved neurocognitive outcomes have been observed in children whose mothers received folic acid supplementation prior to and throughout pregnancy. The analysis does not support a more specific dose recommendation beyond at least 0.4 mg daily. There is limited evidence from a published analysis of 27,784 children born to people with epilepsy that exposure to periconceptional folic acid ≥1 mg/d was associated with a 0.9% absolute increase in the risk of childhood cancer before age 20 years, resulting in a hazard ratio of 2.7 (95% CI 1.2–6.3). Sub analysis restricted to exposure to maternal epilepsy and supplemental folic acid doses <3 mg/d was not significant when compared to maternal epilepsy without a prescription for high-dose folic acid (aHR 2.6, 95% CI 1.0–6.9).[99] A study of 1,257 mother-child pairs from the general population found that very high maternal serum folic acid concentrations (≥60.3 nmol/L) at birth had a 2.5 times increased risk of ASD (95% CI 1.3–4.6) compared to those with lower folic acid

concentrations.[100] These results are concerning, but the studies have some limitations, including their high risk of confounding by indication. The dose chosen should balance demonstrated benefits of supplementation and potential negative consequences of high doses. Future well-designed (preferably randomized) studies are needed to better define optimal folic acid dosing for PWECP.

PRACTICE RECOMMENDATIONS

General

Recommendation 1 rationale

The overarching goals of care for PWECP are to optimize health outcomes both for individuals and their future offspring. In many cases, in utero ASM exposure may be associated with increased risks to the unborn fetus. There are also risks associated with discontinuing or changing ASMs in PWECP.[80, 101-103] A shared decision-making process leads to more informed choices, a better understanding of available options, a more accurate risk perception, and improved decision quality grounded in individual values.[104] This decision-making process may take into account an individual's plans for pregnancy. However, according to the Epilepsy Birth Control Registry of 1,114 PWECP in the United States, more than 65% of pregnancies among PWECP are unintended.[105, 106] The ASM regimen employed for a PWECP when pregnancy is not planned is thus very often the regimen used at the time of conception.

Recommendation 1 statements

1A. Clinicians should engage in joint decision-making with PWECP, taking individual preferences into account when selecting ASMs and monitoring their dosing (Level B).

1B. When treating PWECP, clinicians should recommend ASM(s) and doses that optimize both seizure control and fetal outcomes should pregnancy occur, at the earliest possible opportunity preconceptionally (e.g., at the time of starting an ASM in a person post-menarche) (Level B).

Recommendation 2 rationale

The odds of mortality during pregnancy is 5–12 times greater among PWECP as compared to pregnant people without epilepsy, according to an analysis of a Danish cohort of more than 2 million pregnancies and a US cohort of more than 20 million participants.[107, 108] Among 202 pregnancy-related deaths in the United Kingdom from 2013–2015, the majority of the 13 epilepsy-related deaths were from sudden unexpected death in epilepsy (SUDEP). All participants with pre-pregnancy data had uncontrolled seizures. Five of the participants who died had stopped taking their ASMs during pregnancy.[109]

In an analysis of the EURAP study including 1,956 pregnancies among 1,882 participants, there was no statistical association between seizures during pregnancy and spontaneous abortion or stillbirth. However, the 1 stillbirth that occurred soon after a seizure was an episode of convulsive status epilepticus.[110] The frequency of generalized tonic-clonic seizures or focal to bilateral tonic-clonic seizures may also be a risk factor for lower IQ in children born to PWECP.[80]

Valproic acid is one of the most effective ASMs at obtaining adequate seizure control among people with idiopathic generalized epilepsy.[102, 103] An analysis of the EURAP cohort of PWECP treated with valproic acid at the onset of pregnancy showed that generalized tonic-clonic seizures or focal to bilateral tonic-clonic seizures during pregnancy were twice as likely to occur when the valproic acid was removed or replaced with another ASM, compared to when it was maintained throughout the pregnancy.[101]

The serum concentration of most ASMs has a defined therapeutic window for effective seizure control. The serum concentration of some ASMs (in particular, lamotrigine and levetiracetam) decreases during pregnancy. These decreases may occur at any point during the pregnancy.[111-113]

There are limited data available on epilepsy-related outcomes during pregnancy among PWECP for numerous ASMs including, but not limited to, acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, and vigabatrin.

Recommendation 2 statements

2A. Clinicians must minimize the occurrence of convulsive seizures (generalized tonic-clonic seizures and focal to bilateral tonic-clonic seizures) in PWECP during pregnancy to minimize potential risks to the birth parent (e.g., seizure-related mortality) and to the fetus (Level A).

2B. Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal to bilateral tonic-clonic seizures, even if it is not an optimal choice with regards to the risk to the fetus (e.g., valproic acid) (Level B).

2C. Clinicians should monitor ASM levels in PWECP throughout pregnancy as guided by individual ASM pharmacokinetics and patient clinical presentation (Level B).

2D. Clinicians should adjust the dose of ASMs at their clinical discretion during the pregnancy in response to 1) decreasing serum ASM levels, or 2) worsening seizure control (observed or anticipated based on the clinician's judgment and known pharmacokinetics of ASMs in the pregnant state) (Level B).

2E. Clinicians treating PWECP using acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin should counsel their patients that there are limited data on pregnancy-related outcomes for these drugs (Level B).

Antiseizure medications: Major congenital malformations

Recommendation 3 rationale

The unadjusted birth prevalence of any MCM among children born to people without epilepsy is approximately 2.4%–2.9%.[3] Of the ASMs with sufficient numbers of exposures to draw reliable conclusions (greater than 1,000 exposures), lamotrigine, levetiracetam, and oxcarbazepine are associated with the lowest unadjusted birth prevalence of any MCM in monotherapy (3.1%, 3.5%, and 3.1%, respectively) among children born to PWECP. Valproic acid exposure is associated with the highest unadjusted birth prevalence (9.7%) of any MCM among children born to PWECP as compared to other ASMs.

Valproic acid is associated with the highest unadjusted birth prevalence of NTDs (1.4%) as compared to other ASMs. Phenobarbital is associated with the highest unadjusted birth prevalence of cardiac malformations (4.4%) as compared to other ASMs. Phenobarbital and topiramate are associated with the highest unadjusted birth prevalence of oral and cleft palate (2.2% and 1.4% respectively) compared to other ASMs. Valproic acid is associated with the highest unadjusted birth prevalence of urogenital (1.2%) and renal (1.4%) malformations compared to other ASMs.

A detailed anatomical ultrasound of the fetus can enable earlier diagnosis of MCMs.[114-118] Early detection of severe congenital heart defects, especially those requiring surgery in the early postnatal period, has been shown to improve morbidity and mortality in affected newborns.[119-122] Detection of MCMs can also inform an early pregnancy termination decision or guide perinatal management, including giving birth in specialized pediatric centers, while a normal ultrasound may offer reassurance to expecting parents. This needs to be balanced with differences in individual preferences.

Recommendation 3 statements

3A. Clinicians must counsel their patients with epilepsy that the birth prevalence of any MCM in the general population is approximately 2.4%–2.9%, providing a comparison framework for their individual risk (Level A).

3B. Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in PWECP when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs (Level A).

3C. Clinicians must avoid the use of valproic acid in PWECP to minimize the risk of MCMs (composite outcome) or NTDs, if clinically feasible (Level A).

3D. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that the risk of any MCM is the highest with valproic acid as compared to other studied ASMs (Level A).

3E. To reduce the risk of cardiac malformations, clinicians must avoid the use of phenobarbital in PWECP, if clinically feasible (Level A).

3F. To reduce the risk of oral clefts, clinicians should avoid the use of phenobarbital and topiramate in PWECP, if clinically feasible (Level B).

3G. To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid in PWECP, if clinically feasible (Level B).

3H. To enable early detection and timely intervention of MCMs, obstetricians should recommend fetal screening for MCMs (e.g., a detailed anatomical ultrasound, where available) for PWECP who are treated with any ASM during pregnancy (Level B).

3I. To enable early detection and timely intervention of congenital heart defects, obstetricians should recommend screening cardiac investigations of the fetus among PWECP who are treated with phenobarbital during pregnancy (Level B).

Antiseizure medications: Perinatal outcomes

Recommendation 4 rationale

Among children exposed to ASMs in utero and born to PWECP, the prevalence of intrauterine death is highly likely not to differ across ASMs when used in monotherapy and the prevalence of prematurity is possibly no different across ASMs when used in monotherapy. The risk of intrauterine death is likely higher with polytherapy exposure compared to monotherapy exposure. Fetal growth restriction increases the risk of perinatal morbidity and mortality.[123, 124] The prevalence of children born SGA is possibly greater after exposure to valproic acid or topiramate compared to lamotrigine. Prenatal identification of fetuses at risk of being born SGA leads to improved perinatal outcomes by informing timely delivery.[125]

Recommendation 4 statements

4A. Clinicians should counsel PWECP that the prevalence of intrauterine death does not differ among different ASM exposures in monotherapy (Level B).

4B. Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born SGA, if clinically feasible (Level B).

4C. To enable early identification of fetal growth restriction, obstetricians should recommend screening of fetal growth throughout pregnancy among PWECP who are treated with valproic acid or topiramate (Level B).

Antiseizure medications: Neurodevelopmental outcomes

Recommendation 5 rationale

Among children born to PWECP, in utero exposure to valproic acid is likely associated with a decrease in full scale IQ at age 6 years compared to gabapentin and lamotrigine in monotherapy; valproic acid is possibly associated with a decrease as compared to carbamazepine, levetiracetam, and topiramate in monotherapy; and there is possibly no difference in full scale IQ with valproic acid as compared to phenytoin in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid is likely associated with a decrease in verbal IQ at age 6 years compared to exposure to gabapentin, lamotrigine, levetiracetam, and phenytoin in monotherapy, and is possibly associated with a decrease as compared to carbamazepine and topiramate in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid is possibly associated with a decrease in non-verbal IQ at age 6 years compared to carbamazepine and phenytoin in monotherapy, but there is possibly no difference as compared to gabapentin, lamotrigine, levetiracetam, and topiramate in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid throughout the pregnancy is possibly associated with an increased risk of ASD and autistic traits compared to other studied ASMs (i.e., carbamazepine, clonazepam, lamotrigine, and levetiracetam) used in monotherapy.

Numerous ASMs have limited available data on neurodevelopmental outcomes. These neurodevelopmental outcomes are determined during both early and later stages of pregnancy.[126] Early screening for neurodevelopmental disorders in children enables early diagnosis, facilitating access to early interventions where available. Early interventions in children with neurodevelopmental disorders optimize developmental trajectories.

Recommendation 5 statements

5A. To reduce the risk of poor neurodevelopmental outcomes, including ASD and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in PWECP, if clinically feasible (Level A).

5B. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is likely or possibly associated with a decrease in full-scale, verbal, and non-verbal IQ, as compared to other studied ASMs (i.e., carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, and topiramate) (Level A).

5C. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is possibly associated with an increased risk of ASD as compared to other studied ASMs (i.e., carbamazepine, clonazepam, levetiracetam, and lamotrigine) (Level A).

5D. Clinicians should implement age-appropriate developmental screening in children exposed to any ASM in utero born to PWECP (Level B).

Folic acid

Recommendation 6 rationale

The optimal dosing and timing of folic acid supplementation is unknown in PWECP. There is likely no demonstrated benefit of folic acid supplementation (at least 0.4 mg/d) specifically for the prevention of MCMs in children born to PWECP. Randomized controlled trials conducted before widespread folic acid fortification of foods in the United States demonstrated a reduction in NTDs among the offspring of the general childbearing population receiving periconceptional multivitamin supplementation.[127] A systematic review of 14 studies of folic acid supplementation (up to 1 mg/d) among pregnant people in the general population (generally without epilepsy), including 1,053 participants (some being control participants without folic acid supplementation) estimated that folic acid supplementation of 0.2 mg/d (the United States' level of folic acid fortification), would reduce the risk of NTDs by 23%.[128] This protective effect was greater in pregnant people with an initial low serum folate concentration than in those with higher serum folate concentrations.[128] Although valproic acid exposure in utero is associated with the highest prevalence of NTDs, the teratogenic causal pathway is not exclusively through the disruption of folic acid metabolism.[129]

Preconception folic acid supplementation is possibly associated with better neurodevelopmental outcomes among children born to PWECP. Folic acid supplementation of at least 0.4 mg/d is possibly associated with reduced autistic traits at 3 years (OR 7.9, 95% CI 2.5–24.9) and likely associated with a higher global IQ (on average 6 points) at 6 years in children born to PWECP exposed to ASMs in utero. Lower plasma concentrations of folic acid at gestational weeks 17–19 among pregnant people with epilepsy exposed to ASMs is correlated with a higher risk of autistic traits at 3 years. Higher exposure levels of folic acid from diet and supplements is associated with a statistically significant increases in IQ at age 6 years; this association is not seen among PWECP who only received dietary folic acid and not periconceptional folic acid supplements. Higher doses of folic acid supplementation result in higher serum concentrations of

folic acid.[130, 131] There is inconclusive evidence for an increased risk of adverse events with folic acid supplementation for the PWECP as well as the child (e.g., increased occurrence of twins, asthma, masking vitamin B12 deficiency, new or worsening of pre-existing neoplasia).[99, 127, 132] In a recent analysis of 27,784 children born to people with epilepsy, exposure to periconceptional folic acid greater than 1 mg/d was associated with a 0.9% absolute increase in the risk of childhood cancer before age 20 years, resulting in an HR of 2.7 (95% CI 1.2–6.3).[99] There are potential pharmacokinetic interactions where folic acid can decrease phenytoin serum concentrations.[133] Adherence to folic acid supplementation is generally poor among PWECP, even during pregnancy.[134] ASM polytherapy is associated with decreased folic acid adherence among PWECP.[135] In the United States, where there is no high-dose folic acid formulation, higher doses of folic acid require a large number of tablets, potentially reducing adherence to folic acid supplementation.

Recommendation 6 statements

6A. Clinicians should prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to decrease the risk of NTDs in the offspring (Level B).

6B. Clinicians must prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to possibly improve neurodevelopmental outcomes such as ASD and global IQ in the offspring (Level A).

6C. Clinicians should counsel PWECP treated with an ASM that adherence to recommended folic acid supplementation preconceptionally and during pregnancy is important to minimize the risk of MCMs and poor neurodevelopmental outcomes (Level B).

SUGGESTIONS FOR FUTURE RESEARCH

The findings of this systematic review highlight several knowledge gaps that should be addressed in future research to optimize reproductive outcomes for PWECP. The risks of MCMs and adverse perinatal outcomes for newer and understudied ASMs (e.g., lacosamide, zonisamide, clobazam, and perampanel) require further research. Future guidelines should consider even newer ASMs, such as cenobamate and fenfluramine, which were not included in our search strategy. Longitudinal studies evaluating long-term neurodevelopmental outcomes in children with in utero exposure to ASMs other than valproic acid are necessary to inform ASM choice among PWECP, developmental screening requirements, and resource planning. The risk of MCMs, adverse perinatal outcomes, and adverse neurodevelopmental outcomes in polytherapy is a complex picture that merits further clarification. Importantly, an improved understanding of the pathophysiologic mechanisms underlying teratogenic effects of some ASMs will guide rational development of therapeutic strategies. Clarification of factors affecting the pharmacokinetics and pharmacodynamics of ASM metabolism in PWECP during pregnancy and postpartum will

inform dosing regimens. Future studies should work to use more uniform definitions for exposures (e.g., high vs low doses of ASMs) and outcomes, as well as which adjustment variables are included in any multivariable analyses, to facilitate the discovery of important findings and their interpretation.

There is considerable practice variation in the dosing of folic acid supplementation. High quality studies, including randomized controlled trials where possible, will be required to definitively clarify the optimal dose and timing with respect to conception.

The impact of screening for fetal anomalies and growth restriction on perinatal outcomes needs to be established. Clarification of the impact of socioeconomic status on pregnancy outcomes in PWECP will inform social services priorities. To better clarify the potentially diverse needs of underrepresented groups, future studies should work to include diverse ethnic and racial groups, people from low- and middle-income countries, as well as transgender, nonbinary, and intersex PWECP. Altogether, these lines of research will help identify pregnancies at greatest risk of adverse outcomes and inform new, targeted interventions to improve parental, fetal, perinatal, and neurodevelopmental outcomes.

eAppendix 1. Complete Guideline

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews, and other guidance published by the American Academy of Neurology (AAN) and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. The AAN provides this information on an "as is" basis and makes no warranty, expressed or implied, regarding the information. The AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical, and trustworthy clinical practice guidelines (CPGs) and evidence-based documents. Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this evidence-based document. Management and disclosure of document developer relationships is conducted in compliance with the 2017 AAN process manual section titled, "Implementing the AAN Conflict of Interest Policy for Guidelines and Case Definitions," which can be viewed at www.aan.com.

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eAppendix 1. Complete Guideline

APPENDICES

Appendix 1. AAN Guidelines Subcommittee mission

The mission of the Guidelines Subcommittee is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The Guidelines Subcommittee is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix 2. Guidelines Subcommittee members 2021-2023

Alexander Rae-Grant, MD (Chair), John J. Halperin, MD (Vice-Chair), Matthew Bradford Bevers, MD, Lori L. Billinghurst, MD, Kelsey Cacic, MD, James Dorman, MD, Wendy S. Edlund, MD, Brittany Jade Farro, MSPAS, PA-C, Gary S. Gronseth, MD, FAAN, Le Hua, MD, Koto Ishida, MD, Mark Douglas Johnson, MD, Charles Kassardjian, MD, Mark Robert Keezer, MD, PhD, K.H. Vincent Lau, MD, Mia T. Minen, MD, Alison M. Pack, MD, Sonja Potrebic, MD, PhD, James J. Reese, Jr., MD, MPH, Sean C. Rose, MD, Vishwanath Sagi, MD, Navdeep Sangha, MD, Nicolaos Scarmeas, MD, Niranjan N. Singh, MD, Sarah Tanveer, Benjamin D. Tolchin, MD, Shawniqua T. Williams Roberson, MD, Shuhan Zhu, MD

Appendix 3. Complete search strategy

1. Databases to be searched (e.g. MEDLINE, EMBASE): MEDLINE, CENTRAL, CDSR, EMBASE, CINAHL, DARE, ClinicalTrials.gov, FDA literature
2. Years to be included: June 1, 2007 to February 15, 2019 (June 2007 was cut-off of previous guideline)
3. Keywords
    i. Disease and population keywords: Epilepsy AND seizure AND (pregnant women OR pregnancy)
    ii. Intervention keywords:
        - Folic acid OR Folvite OR Folacin OR Folate OR Vitamin B9
        - Anti-epileptic drugs OR AEDs OR anticonvulsants OR:
            a. Acetazolamide
            b. Carbamazepine
            c. Clobazam
            d. Clonazepam
            e. Eslicarbazepine acetate
            f. Ethosuximide
            g. Gabapentin
            h. Lacosamide

i. Lamotrigine
j. Levetiracetam
k. Nitrazepam
l. Oxcarbazepine
m. Perampanel
n. Piracetam
o. Phenobarbital
p. Phenytoin
q. Pregabalin
r. Primidone
s. Rufinamide
t. Sodium valproate
u. Stiripentol
v. Tiagabine
w. Topiramate
x. Vigabatrin
y. Zonisamide

iii. Outcome keywords:

- Major congenital malformations OR congenital abnormalities OR Abnormalities, drug induced
- Autism OR Autism Spectrum Disorder OR Autistic Disorder OR Asperger Syndrome
- Cognitive disabilities OR cognition disorders OR learning disabilities OR learning disorders OR dyscalculia OR dyslexia
- Miscarriage OR spontaneous abortion
- Small for gestational age OR Infant, Small for Gestational Age OR Infant, low birth weight
- Small head circumference OR microcephaly
- Early labor OR Labor, Preterm OR Labor, Premature OR Premature Obstetric Labor OR Premature Birth

4. Inclusion and Exclusion Criteria

a) **Languages:**
☒ All languages
☐ English language only

b) **Selected Study Population**
i. Humans: ☒Include ☐ Exclude
ii. Animal studies: ☐Include ☒Exclude

iii. Sex:

☒Females

☐Males

iv. Age:

☐Children only (if checked, specify age range: __ to __)

☒Adults only (women age 18+ of child-bearing potential)

☐Both adults and children

c) **Disease in question or closely related to diseases to be**
   - **i.** Include: Epilepsy
   - **ii.** Exclude: None

d) **Interventions to be**:
   - **i.** Include: AEDs, folic acid
   - **ii.** Exclude: None

e) **Outcomes to be**:
   - **i.** Include: Major congenital malformations, autism, cognitive disabilities, learning disabilities, seizure increase, miscarriage, small for gestational age, small head circumference, bleeding during pregnancy, early labor, hemorrhagic disease of the newborn,.
   - **ii.** Exclude: None

f) **Types of studies to be included:**

☐ **Randomized Control Trial**

☒ **Cohort – Prospective**

☒ **Cohort – Retrospective**

☒ **Case Control**

☒ **Case Series**

☒ **Review Papers/SRs** (for cross checking references only)

☒ **Meta-analyses**

g) **Standard exclusion criteria:**
   - **i.** Not relevant to the clinical question
   - **ii.** Unrelated disease
   - **iii.** Outside of study population
     - i) Males
     - ii) Women who are NOT pregnant
   - **iv.** Articles not peer-reviewed

h) **Additional exclusion criteria:**
   - **i.** None

Appendix 4. Evidence profile tables

eAppendix 1. Complete Guideline

The evidence profile tables are available from the AAN, by request.

Appendix 5. Evidence synthesis tables

The evidence synthesis tables are available from the AAN, by request.

Appendix 6. Rationale of factors considered in developing the practice recommendations

In this appendix, EVID refers to evidence systematically reviewed; RELA to strong evidence derived from related conditions; PRIN to axiomatic principles of care; and INFER to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based.

General

Recommendation 1 rationale

The overarching goals of care for PWECP are to optimize health outcomes both for individuals and their future offspring (PRIN). In many cases, in utero ASM exposure may be associated with increased risks to the unborn fetus (EVID). There are also risks associated with discontinuing or changing ASMs in PWECP (RELA).[80, 101-103] A shared decision-making process leads to more informed choices, a better understanding of available options, a more accurate risk perception, and improved decision quality grounded in individual values (PRIN).[104] This decision-making process may take into account an individual's plans for pregnancy (PRIN). However, according to the Epilepsy Birth Control Registry of 1,114 PWECP in the United States, more than 65% of pregnancies among PWECP are unintended (RELA).[105, 106] The ASM regimen employed for a PWECP when pregnancy is not planned is thus very often the regimen used at the time of conception (INFER).

Recommendation 1 statements

1A. Clinicians should engage in joint decision-making with PWECP, taking individual preferences into account when selecting ASMs and monitoring their dosing (Level B).

1B. When treating PWECP, clinicians should recommend ASM(s) and doses that optimize both seizure control and fetal outcomes should pregnancy occur, at the earliest possible opportunity preconceptionally (e.g., at the time of starting an ASM in a person post-menarche) (Level B).

Recommendation 2 rationale

The odds of mortality during pregnancy is 5–12 times greater among PWECP as compared to pregnant people without epilepsy, according to an analysis of a Danish cohort of more than 2 million pregnancies and a US cohort of more than 20 million participants (RELA).[107, 108] Among 202 pregnancy-related deaths in the United Kingdom from 2013–2015, the majority of the 13 epilepsy-related deaths were from sudden unexpected death in epilepsy (SUDEP). All participants with pre-pregnancy data had uncontrolled seizures. Five of the participants who died had stopped taking their ASMs during pregnancy (RELA).[109]

In an analysis of the EURAP study including 1,956 pregnancies among 1,882 participants, there was no statistical association between seizures during pregnancy and spontaneous abortion or stillbirth. However, the 1 stillbirth that occurred soon after a seizure was an episode of convulsive status epilepticus (RELA).[110] The frequency of generalized tonic-clonic seizures or focal to bilateral tonic-clonic seizures may also be a risk factor for lower IQ in children born to PWECP (RELA).[80]

Valproic acid is one of the most effective ASMs at obtaining adequate seizure control among people with idiopathic generalized epilepsy (RELA).[102, 103] An analysis of the EURAP cohort of PWECP treated with valproic acid at the onset of pregnancy showed that generalized tonic-clonic seizures or focal to bilateral tonic-clonic seizures during pregnancy were twice as likely to occur when the valproic acid was removed or replaced with another ASM, compared to when it was maintained throughout the pregnancy (RELA).[101]

The serum concentration of most ASMs has a defined therapeutic window for effective seizure control (PRIN). The serum concentration of some ASMs (in particular, lamotrigine and levetiracetam) decreases during pregnancy. These decreases may occur at any point during the pregnancy (RELA).[111-113]

There are limited data on epilepsy-related outcomes during pregnancy among PWECP available for multiple ASMs, including but not limited to acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, and vigabatrin (EVID).

Recommendation 2 statements

2A. Clinicians must minimize the occurrence of convulsive seizures (generalized tonic-clonic seizures and focal to bilateral tonic-clonic seizures) in PWECP during pregnancy to minimize potential risks to the birth parent (e.g., seizure-related mortality) and to the fetus (Level A).

2B. Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal to bilateral tonic-clonic seizures, even if it is not an optimal choice with regards to the risk to the fetus (e.g., valproic acid) (Level B).

2C. Clinicians should monitor ASM levels in PWECP throughout pregnancy as guided by individual ASM pharmacokinetics and patient clinical presentation (Level B).

2D. Clinicians should adjust the dose of ASMs at their clinical discretion during the pregnancy in response to 1) decreasing serum ASM levels, or 2) worsening seizure control (observed or anticipated based on the clinician's judgment and known pharmacokinetics of ASMs in the pregnant state) (Level B).

2E. Clinicians treating PWECP using acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin should counsel their patients that there are limited data on pregnancy-related outcomes for these drugs (Level B).

Antiseizure medications: Major congenital malformations

Recommendation 3 Rationale

The unadjusted birth prevalence of any MCM among children born to people without epilepsy is approximately 2.4%–2.9% (RELA).[3] Of the ASMs with sufficient numbers of exposures to draw reliable conclusions (greater than 1,000 exposures), lamotrigine, levetiracetam, and oxcarbazepine are associated with the lowest unadjusted birth prevalence of any MCM in monotherapy (3.1%, 3.5%, and 3.1%, respectively) among children born to PWECP (EVID). Valproic acid exposure is associated with the highest unadjusted birth prevalence (9.7%) of any MCM among children born to PWECP, as compared to other ASMs (EVID).

Valproic acid is associated with the highest unadjusted birth prevalence of NTDs (1.4%) as compared to other ASMs (EVID). Phenobarbital is associated with the highest unadjusted birth prevalence of cardiac malformations (4.4%) as compared to other ASMs (EVID). Phenobarbital and topiramate are associated with the highest unadjusted birth prevalence of oral and cleft palate (2.2% and 1.4% respectively) compared to other ASMs (EVID). Valproic acid is associated with the highest unadjusted birth prevalence of urogenital (1.2%) and renal (1.4%) malformations compared to other ASMs (EVID).

A detailed anatomical ultrasound of the fetus can enable earlier diagnosis of MCMs.[114-118] Early detection of severe congenital heart defects, especially those requiring surgery in the early postnatal period, has been shown to improve morbidity and mortality in affected newborns (RELA).[119-122] Detection of MCMs can also inform an early pregnancy termination decision or guide perinatal management, including giving birth in specialized pediatric centers, while a normal ultrasound may offer reassurance to expecting parents. This needs to be balanced with differences in individual preferences. (PRIN)

Recommendation 3 Statements

3A. Clinicians must counsel their patients with epilepsy that the birth prevalence of any MCM in the general population is approximately 2.4%–2.9%, providing a comparison framework for their individual risk (Level A).

3B. Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in PWECP when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs (Level A).

3C. Clinicians must avoid the use of valproic acid in PWECP to minimize the risk of MCMs (composite outcome) or NTDs, if clinically feasible (Level A).

3D. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that the risk of any MCM is the highest with valproic acid as compared to other studied ASMs (Level A).

3E. To reduce the risk of cardiac malformations, clinicians must avoid the use of phenobarbital in PWECP, if clinically feasible (Level A).

3F. To reduce the risk of oral clefts, clinicians should avoid the use of phenobarbital and topiramate in PWECP, if clinically feasible (Level B).

3G. To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid in PWECP, if clinically feasible (Level B).

3H. To enable early detection and timely intervention of MCMs, obstetricians should recommend fetal screening for MCMs (e.g., a detailed anatomical ultrasound, where available) for PWECP who are treated with any ASM during pregnancy (Level B).

3I. To enable early detection and timely intervention of congenital heart defects, obstetricians should recommend screening cardiac investigations of the fetus among PWECP who are treated with phenobarbital during pregnancy (Level B).

Antiseizure medications: Perinatal outcomes

Recommendation 4 rationale

Among children exposed to ASMs in utero and born to PWECP, the prevalence of intrauterine death is highly likely not to differ across ASMs when used in monotherapy (EVID) and the prevalence of prematurity is possibly no different across ASMs when used in monotherapy (EVID). The risk of intrauterine death is likely higher with polytherapy exposure compared to monotherapy exposure (EVID). Fetal growth restriction increases the risk of perinatal morbidity and mortality (RELA).[123, 124] The prevalence of children born SGA is possibly greater after exposure to valproic acid or topiramate compared to lamotrigine (EVID). Prenatal identification of fetuses at risk of being born SGA leads to improved perinatal outcomes by informing timely delivery (RELA).[125]

Recommendation 4 statements

4A. Clinicians should counsel PWECP that the prevalence of intrauterine death does not differ among different ASM exposures in monotherapy (Level B).

4B. Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born SGA, if clinically feasible (Level B).

4C. To enable early identification of fetal growth restriction, obstetricians should recommend screening of fetal growth throughout pregnancy among PWECP who are treated with valproic acid or topiramate (Level B).

Antiseizure medications: Neurodevelopmental outcomes

Recommendation 5 rationale

Among children born to PWECP, in utero exposure to valproic acid is likely associated with a decrease in full scale IQ at age 6 years compared to gabapentin and lamotrigine in monotherapy; valproic acid is possibly associated with a decrease as compared to carbamazepine, levetiracetam, and topiramate in monotherapy; and there is possibly no difference in full scale IQ with valproic acid as compared to phenytoin in monotherapy (EVID).

Among children born to PWECP, in utero exposure to valproic acid is likely associated with a decrease in verbal IQ at 6 years of age compared to exposure to gabapentin, lamotrigine, levetiracetam, and phenytoin in monotherapy, and is possibly associated with a decrease as compared to carbamazepine and topiramate in monotherapy (EVID).

Among children born to PWECP, in utero exposure to valproic acid is possibly associated with a decrease in non-verbal IQ at 6 years of age compared to carbamazepine and phenytoin in monotherapy, but there is possibly no difference as compared to gabapentin, lamotrigine, levetiracetam, and topiramate in monotherapy (EVID).

Among children born to PWECP, in utero exposure to valproic acid throughout the pregnancy is possibly associated with an increased risk of ASD and autistic traits compared to other studied ASMs (i.e., carbamazepine, clonazepam, lamotrigine, and levetiracetam) used in monotherapy (EVID).

Numerous ASMs have limited available data on neurodevelopmental outcomes (EVID). These neurodevelopmental outcomes are determined during both early and later stages of pregnancy (RELA).[126] Early screening for neurodevelopmental disorders in children enables early diagnosis, facilitating access to early interventions where available (PRIN). Early interventions in children with neurodevelopmental disorders optimize developmental trajectories (PRIN).

Recommendation 5 statements

5A. To reduce the risk of poor neurodevelopmental outcomes, including ASD and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in PWECP, if clinically feasible (Level A).

5B. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is likely or possibly associated with a decrease in full-scale, verbal, and non-verbal IQ, as compared to other studied ASMs (i.e., carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, and topiramate) (Level A).

5C. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is possibly associated with an increased risk of ASD as compared to other studied ASMs (i.e., carbamazepine, clonazepam, oxcarbazepine, and lamotrigine) (Level A).

5D. Clinicians should implement age-appropriate developmental screening in children exposed to any ASM in utero born to PWECP (Level B).

Folic acid

Recommendation 6 rationale

The optimal dosing and timing of folic acid supplementation is unknown in PWECP (EVID). There is likely no demonstrated benefit of folic acid supplementation (at least 0.4 mg/d) specifically for the prevention of MCMs in children born to PWECP (EVID). Randomized controlled trials conducted before widespread folic acid fortification of foods in the United States demonstrated a reduction in NTDs among the general childbearing population receiving periconceptional multivitamin supplementation (RELA).[127] A systematic review of 14 studies of folic acid supplementation (up to 1 mg/d) among pregnant people in the general population(generally without epilepsy), including 1,053 participants (some being control participants without folic acid supplementation) estimated that folic acid supplementation of 0.2

mg/d (the United States' level of folic acid fortification), would reduce the risk of NTDs by 23%.[128] This protective effect was greater in pregnant people with an initial low serum folate concentration than in those with higher serum folate concentrations (RELA).[128] Although valproic acid exposure in utero is associated with the highest prevalence of NTDs (EVID), the teratogenic causal pathway is not exclusively through the disruption of folic acid metabolism (RELA).[129]

Preconception folic acid supplementation is possibly associated with better neurodevelopmental outcomes among children born to PWECP (EVID). Folic acid supplementation of at least 0.4 mg/d is possibly associated with reduced autistic traits at 3 years (OR 7.9, 95% CI 2.5–24.9) and likely associated with a higher global IQ (on average 6 points) at 6 years in children born to PWECP exposed to ASMs in utero (EVID). Lower plasma concentrations of folic acid at gestational weeks 17–19 among pregnant PWECP exposed to ASMs is correlated with a higher risk of autistic traits at 3 years (EVID). Higher exposure levels of folic acid from diet and supplements is associated with statistically significant increases in IQ at age 6 years; this association is not seen among PWECP who only received dietary folic acid and not periconceptional folic acid supplements (EVID). Higher doses of folic acid supplementation result in higher serum concentrations of folic acid (RELA).[130, 131] There is inconclusive evidence for an increased risk of adverse events with folic acid supplementation for the PWECP as well as the child (e.g., increased occurrence of twins, asthma, masking vitamin B12 deficiency, new or worsening of pre-existing neoplasia) (RELA).[99, 127, 132] In a recent analysis of 27,784 children born to people with epilepsy, exposure to periconceptional folic acid greater than 1 mg/d was associated with a 0.9% absolute increase in the risk of childhood cancer before age 20 years, resulting in an HR of 2.7 (95% CI 1.2–6.3).[99] There are potential pharmacokinetic interactions where folic acid can decrease phenytoin serum concentrations (RELA).[133] Adherence to folic acid supplementation is generally poor among PWECP, even during pregnancy (RELA).[134] ASM polytherapy is associated with decreased folic acid adherence among PWECP (RELA).[135] In the United States, where there is no high-dose folic acid formulation, higher doses of folic acid require a large number of tablets, potentially reducing adherence to folic acid supplementation (INFER).

Recommendation 6 statements

6A. Clinicians should prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to decrease the risk of NTDs in the offspring (Level B).

6B. Clinicians must prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to possibly improve neurodevelopmental outcomes such as ASD and global IQ in the offspring (Level A).

6C. Clinicians should counsel PWECP treated with an ASM that adherence to recommended folic acid supplementation preconceptionally and during pregnancy is important to minimize the risk of MCMs and poor neurodevelopmental outcomes (Level B).